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Risk Factors for Postoperative Cognitive Dysfunction in Older Adults Undergoing Major Noncardiac Surgery

Osama Shoair

Virginia Commonwealth University

RISK FACTORS FOR POSTOPERATIVE COGNITIVE DYSFUNCTION IN OLDER ADULTS UNDERGOING MAJOR NONCARDIAC SURGERY

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

By

OSAMA A. SHOAIR

Bachelors in Pharmaceutical Sciences, Misr International University, Cairo, Egypt, 2005

Certificate in Aging Studies, Virginia Commonwealth University, Richmond, Virginia, 2013

Director: PATRICIA W. SLATTUM, PHARM.D., PH.D.

Associate Professor and Director of Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science

Virginia Commonwealth University

Richmond, Virginia

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List of Abbreviations

AD	Alzheimer's disease
ANOVA	Analysis of variance
ApoE4	Apolipoprotein-E4
BDZs	Benzodiazepines
BIS	Bispectral index
CA	Coronary angiography
CABG	Coronary artery bypass grafting
CAM	Confusion Assessment Method
CBP	Cardiopulmonary bypass
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CRP	C-reactive protein
CSI	Cerebral state index
CV	Coefficient of variation
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders (Fourth Edition, Text Revision)
GA	General anesthesia
GDS-SF	Geriatric Depression Scale, Short-Form
ICD	International classification of diseases
IL	Interleukin
IRB	Institutional Review Board
ISPOCD	International Study of Postoperative Cognitive Dysfunction
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
NSE	Neuron-specific enolase
OR	Odds ratio

PACU	Post-anesthesia care unit
PCA	Patient-controlled analgesia
PCI	Preoperative cognitive impairment
PEG	Polyethylene glycol
POCD	Postoperative cognitive dysfunction
POD	Postoperative delirium
PSQI	Pittsburgh Sleep Quality Index
RA	Regional anesthesia
REDCap™	Research Electronic Data Capture
SD	Standard deviation
THJR	Total hip joint replacement
TKA	Total knee arthroplasty
TNF- α	Tumor-necrosis factor-alpha
VCUHS	Virginia Commonwealth University Health System

Abstract

RISK FACTORS FOR POSTOPERATIVE COGNITIVE DYSFUNCTION IN OLDER ADULTS UNDERGOING MAJOR NONCARDIAC SURGERY

By: Osama Ali Shoair, PhD

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Major Director: Patricia W. Slattum, Pharm.D., Ph.D.
Associate Professor and Director of Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science

Background: Postoperative cognitive dysfunction (POCD) is a deterioration in cognitive function that occurs after surgery as measured by neuropsychological tests. The purpose of this study was to determine the incidence and risk factors for POCD in older adults three months after major noncardiac surgery.

Methods: This is a prospective study of patients aged 65 years and older who underwent major noncardiac surgery. Patients' cognitive function was assessed before and three months after surgery using a computerized neurocognitive battery. Blood samples were withdrawn from patients before surgery to identify patients with high level of C-reactive protein (CRP), and patients who had the apolipoprotein-E4 (ApoE4) allele, as potential inflammatory and genetic

biomarkers for POCD, respectively. A nonsurgical control group, that is similar to patients in age, education level, and computer familiarity, was recruited to adjust for learning effects from repeated administration of neurocognitive tests. Patients were classified as having POCD if they had less than -1.96 in the individual *Z*-scores of two or more tests or in the composite *Z*-score.

Results: A total of 69 patients and 54 controls completed the study. The mean age for patients was 71 ± 5.4 (65–88) years old and 66.7% of them were females. The majority of patients (78.3%) had above high school education. There was no difference between the surgical and nonsurgical groups in demographics except for age which was marginally higher in the nonsurgical group [73 ± 6.3 (65-92)].

The incidence of POCD was 15.9% three months after surgery. Multivariable logistic regression showed that carrying the ApoE4 allele (OR = 4.74, 95% CI = 1.09 – 22.19), using one or more highly anticholinergic or sedative-hypnotic drugs at home prior to surgery (OR = 5.64, 95% CI = 1.35 – 30.22), and receiving sevoflurane for anesthesia (OR = 6.43, 95% CI = 1.49 – 34.66) were risk factors for POCD.

Conclusion: The incidence of POCD in older adults is 15.9% three months after major noncardiac surgery. Risk factors for POCD were carrying the ApoE4 allele, using one or more highly anticholinergic or sedative-hypnotic drugs at home prior to surgery, and receiving sevoflurane for anesthesia.

CHAPTER 1: INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a deterioration in cognitive function that occurs to patients after surgery as compared to their preoperative cognitive status. POCD is not a new phenomenon and it has been well-documented in the literature for a very long time. About fifty five years ago, Bedford published a retrospective observational report of 251 older patients over the age of 65 years who experienced deterioration in their cognitive function after surgery as was described by the patients or their family members.[1,2] He observed, without performing any neuropsychological testing, that a minor degree of dementia was present in this group and that 7% of them experienced severe dementia to the extent that he suggested that "operations on elderly people should be confined to unequivocally necessary cases".[1] Most of the research initially focused on POCD in cardiac surgery since the proportion of patients who experienced decline in cognitive function after this type of surgery was large compared to other types of surgery. POCD is now recognized as a potential complication of cardiac surgery and current research is trying to elucidate the risk factors of POCD in this type of surgery, particularly the role of cardiopulmonary bypass (CPB) in contributing to POCD.[3] In contrast, the research about the incidence and risk factors of POCD after noncardiac surgery is still in its infancy, and the results of current research in this area is still conflicting and inconclusive.

I. DEFINITION OF POCD

Currently, there is no consensus definition of POCD in the literature. For research purposes, POCD is generally defined as a decline or deterioration in cognitive function that occurs in patients after surgery when compared to their preoperative cognitive status as measured

by neuropsychological testing. This decline is usually subtle in nature and is observed most of the time by the patients, their caregivers, or close friends. A statement from a patient such as "I am not the same" after surgery can simply represent the patient's lay language of having POCD in the absence of a gold standard tool to diagnose it. POCD can affect different cognitive domains including verbal memory, visual memory, processing speed, cognitive flexibility, and executive function.[4] Due to its often subtle nature, the condition can usually be missed by clinicians, and an appropriate battery of neurocognitive tests, that is sensitive to subtle changes in cognitive function and covers a wide array of cognitive abilities, is necessary to determine if a patient is having POCD.

The risk of POCD may be increased in older adults due to various changes associated with physiology of aging. Cerebral changes occur to the brain as we age including reduction of the complexity of neuronal connections, reduction of the synthesis of neurotransmitters, and increase in the postsynaptic degradation of neurotransmitters.[5] The changes may also include decreased regional brain volume, impaired serotonin, acetylcholine, and dopamine receptor binding and signaling, accumulation of neurofibrillary tangles, and altered concentrations of various brain metabolites.[6-11] There are also pharmacokinetic and pharmacodynamic changes that progressively occur with aging.[12] Pharmacokinetic changes include a reduction in renal and hepatic clearance and increase in volume of distribution of lipid soluble drugs resulting in prolongation of elimination half-life of several drugs.[12] Pharmacodynamic changes involve altered, usually increased, sensitivity to several classes of drugs including medications with anticholinergic and sedative properties that are known to cause negative cognitive outcomes.[12] These changes may also cause the brain of older patients to have less tolerability to anesthetic drugs and other highly anticholinergic and sedative-hypnotic medications during the surgery

which may increase vulnerability of older adult patients to neurologic deterioration and various insults that happen to the brain during surgery.

II. INCIDENCE OF POCD

The reported incidence of POCD in the literature after both cardiac and noncardiac surgery is enormously variable and should be interpreted cautiously. This is due to several factors including the wide variability in the definition of POCD, number of cognitive domains assessed, number and type of neurocognitive tests used to assess each cognitive domain, time of pre- and postoperative assessment of cognitive function, type of surgery and anesthesia, and the use of a control group to adjust for learning effects from repeated administration of neurocognitive tests. The incidence of POCD has been reported to be 30 – 80% a few weeks after cardiac surgery, and 10 – 60% after three to six months.[2] The first International Study of Postoperative Cognitive Dysfunction (ISPOCD1) reported the incidence of POCD after major noncardiac surgery to be 25.8% one week after surgery and 9.9% after 3 months.[13] Newman et al. conducted a meta-analysis showing that the incidence of POCD after noncardiac surgery in studies published until December 2005, ranged between 6.2% and 56% 22 days and up to six months aftersurgery.[1] Ignoring the one study with very high incidence of POCD, the incidence range was between 6.2% and 9.4%.[1] These reports reveal how difficult it is to obtain accurate estimates of the incidence of POCD after different types of surgery. As mentioned earlier, this is due to the wide variability in the methodology used to determine the incidence of POCD. This also makes it very difficult to compare the results of different POCD studies.

III. POSTOPERATIVE DELIRIUM (POD) AND POCD

POCD may be confused with postoperative delirium (POD), and may mistakenly be considered as part of the same continuum. However, despite their similarities, POCD and POD are two distinct phenomena. POD is well defined in the World Health Organization's classification of diseases (ICD-10) and the Diagnostic and Statistical Manual for Mental Disorders [fourth edition, text revision] (DSM-IV-TR).[14] POD is characterized by an acute onset of altered consciousness, disorientation, and confusion which starts hours to days after surgery and can last for days to weeks. In most patients, POD often occurs within the first three days after surgery.[14] Attention is usually impaired in POD and may be associated with fluctuation in consciousness.[14] POD is usually reversible especially if the clinician can determine its underlying cause.[14] POD can be assessed using several valid and reliable tools such as the Confusion Assessment Method (CAM).[15]

On the other hand, POCD does not have a consensus definition or ICD diagnostic codes and its onset is subtle in nature. POCD is generally not well-characterized and the major complaint of patients with POCD would be a general deterioration in memory or other cognitive domains that may make it hard enough for some patients to manage their job or daily activities.[14] The onset of POCD usually occurs within weeks to months after surgery and may last for years or become permanent. The number and type of affected cognitive domains in POCD widely vary, but consciousness is not altered in POCD.[14] POCD may be reversible but it can also be long lasting in some patients.[14] There is no current consensus on the number or type of neurocognitive tests that should be used to diagnose POCD. Table 1 summarizes the major differences between POCD and POD.

IV. LONG-TERM CONSEQUENCES OF POCD

POCD is a serious phenomenon and should not be underestimated by patients, caregivers, or clinicians. Monk et al. showed an association between POCD and increased mortality in patients in the first year after major noncardiac surgery.[17] Patients with POCD at hospital discharge were more likely to die before the three-month follow-up cognitive testing, and patients who continued to have persistent POCD after three months were at higher risk of death in the first year after surgery.[18] Another study showed that POCD after noncardiac surgery was associated with increased mortality, decreased quality of life, risk of early withdrawal from the workforce, and increased dependency on society.[19,20]

Table 1. Summary of Major Differences between POCD and POD (Adapted from Krenk et al.)[14]

Features	POD	POCD
Definition and Severity	ICD-9/10, DSM-IV-TR	Controversial
Incidence	4 – 54%[16]	7 – 71%[1]
Onset	Acute (hours to days)	Subtle (weeks to months)
Duration	Days to weeks	Weeks to years
Cognitive Changes	Attention	Multiple/Variable
Consciousness	Altered	Normal
Reversibility	Usually reversible	May be reversible

V. RISK FACTORS FOR POCD

The mechanisms and risk factors for POCD are still unknown, and POCD is likely a multifactorial condition. The next chapter will discuss three major theories in the current literature that may play a role in the development of POCD. The first theory is related to surgery

and it includes several factors such as type of surgery, possible neuroinflammation during surgery, postoperative delirium, and postoperative complications. The second theory is concerned about medications being administered to the patients including home medications prior to surgery, anesthesia and sedation during surgery, and postoperative analgesics. The third theory puts the 'fault' on the patient and suggests that POCD may be associated with patient's age, education level, predisposition with certain genes related to cognitive deterioration, and other factors. The next chapter will elaborate in detail on each of these variables and the literature supporting it.

VI. SUMMARY

POCD does not have a consensus definition in the literature, but it can be generally defined as a deterioration in patients' cognitive function after surgery compared to their preoperative cognitive status as measured by neuropsychological testing. POCD has primarily been documented after cardiac surgery, but it has been recently reported after noncardiac surgery as well. POCD is usually subtle in nature and may be underestimated by clinicians. The incidence of POCD in the literature widely varies depending on the definition of POCD, number of cognitive domains assessed, number and type of neurocognitive tests used to assess each cognitive domains, time of pre- and postoperative assessment of cognitive function, type of surgery and anesthesia, and the use of a control group to adjust for learning effects. POCD is usually confused with POD after surgery though they are different in the onset, duration, cognitive changes, alteration of consciousness, and possible reversibility. POCD has long-term consequences that may range from decreased quality of life to mortality. The risk factors for POCD are still unknown and POCD is likely to be multifactorial. Potential risk factors for POCD

may be related to surgery, medications, or the patient. The next chapter will discuss these risk factors in detail and the literature supporting them.

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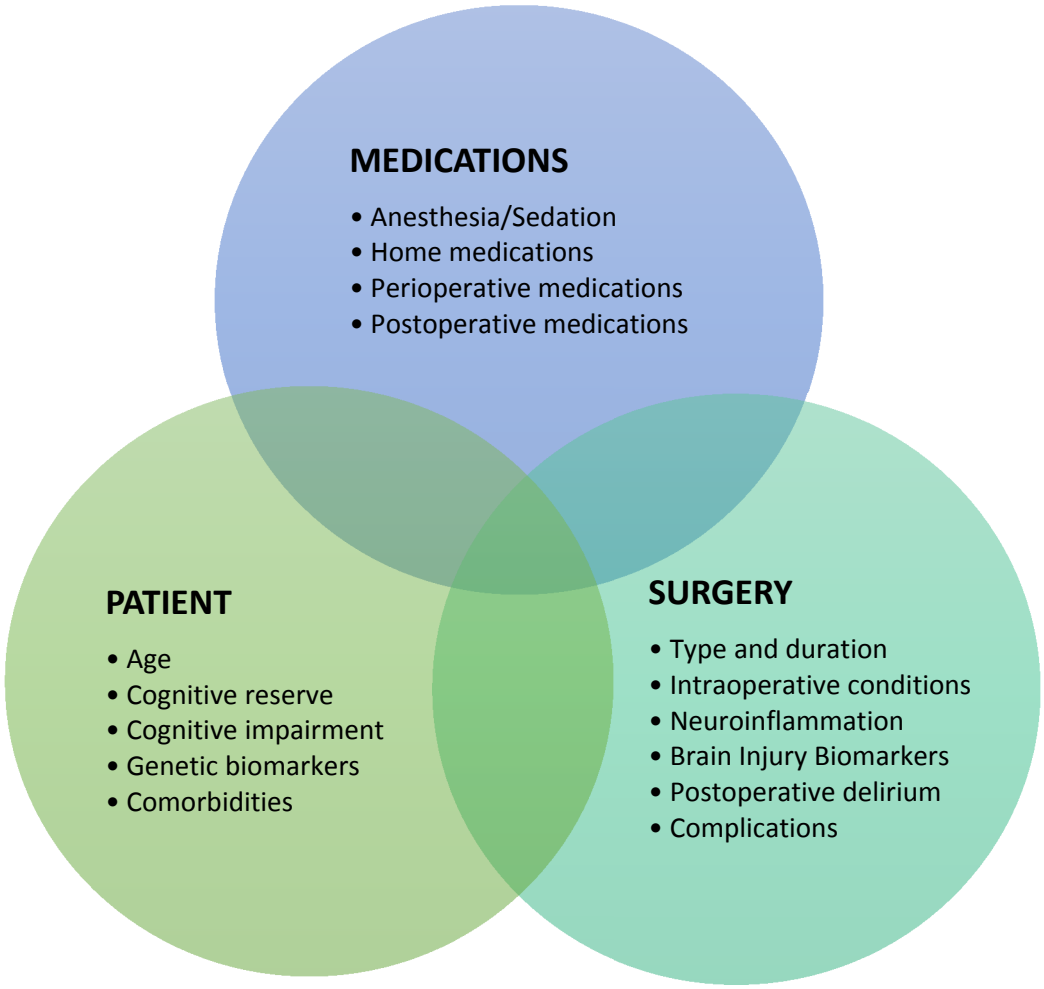
CHAPTER 2: LITERATURE REVIEW

I. ETIOLOGY AND RISK FACTORS OF POCD

The etiology and pathophysiologic mechanisms of POCD remain unknown and POCD is likely a multifactorial condition. Currently, there are three major theories that may explain POCD: medication, surgery, and patient theories.[1,2] Each of these theories includes several potential risk factors for POCD. First, there is the medication theory which suggests that certain anesthetic and sedatives agents administered during and after the surgery may be etiological in POCD, particularly those medications with highly anticholinergic or sedative properties. This theory also extends to medications that the patient has been chronically using at home prior to his admission to surgery. Second is the surgery theory that is inclusive of factors related to the type and duration of the surgery, intraoperative conditions and physiologic changes that occur during the surgery, possible inflammation or traumatic injury to the brain, postoperative delirium, length of hospitalization, and postoperative complications such as infection or respiratory depression. A third theory suggests that it might not be the medication or the surgery theories, and that it is basically the patient's 'fault'.[1] This theory suggests that patients' age, cognitive reserve or the ability to sustain neurologic insults, pre-existing cognitive impairment before surgery, genetic predisposition related to dementia such as the apolipoprotein-E4 (ApoE4) allele, chronic depression or anxiety prior to surgery, alcoholism or chronic smoking, and their comorbidities may be associated with the risk of POCD. Figure 1 shows a summary of the three current major theories and risk factors of POCD. The most important candidate risk factors that might play independent or collaborative roles in the genesis of POCD will be discussed in detail.

Figure 1. Major Theories and Risk Factors of POCD



A. MEDICATIONS

1. Anesthesia/Sedation

The role of general anesthesia (GA) in causing cognitive dysfunction has often been described as a potential risk factor for POCD especially in older adults.[3] Animal studies showed that long exposure to common anesthetic agents can cause cell damage and apoptosis.[4] Jevtovic-Todorovic et al. found cell death in rat brains after exposure to midazolam, nitrous oxide, and isoflurane, and when combining all three agents, there was a significant decline in their memory

and learning skills.[4] However, these observations might not be transferable to humans and there is a need to accumulate evidence in humans to determine if they are related to the type, duration, or depth of anesthesia. Few studies have been conducted to evaluate if there is an association between POCD and the type of anesthesia [general (inhaled, intravenous), regional (spinal, epidural, or nerve block), or both general and regional anesthesia], duration of anesthesia, and depth of anesthesia. Also, there is an increased interest in studying the risk of POCD associated with the use of sedative agents during surgery.

Rasmussen et al. randomized 428 patients aged 60 years and older undergoing major noncardiac surgery for GA versus regional anesthesia (RA).[5] They evaluated patients' cognitive function seven days and three months after surgery finding a significant difference in POCD incidence at seven days between the GA and RA groups [21.2% versus 12.7% (p = 0.04)], respectively.[5] However, at the three-month follow-up, there was no significant difference in the incidence of POCD between the two groups (14.3% after GA and 13.9% after RA).[5] Evered et al. also compared the incidence of POCD three months postoperatively after GA and RA, but they could not find a significant difference (21% vs. 16%, respectively).[6] They concluded that POCD is independent of the type of anesthesia used during the surgery.[6] Mason et al. conducted a meta-analysis to compare the influence of general, regional, or a combination of GA and RA on the development of POCD.[7] They compared the incidence of POCD when patients were administered GA versus individual types of RA and also the combination of GA and RA, but they could not find a significantly higher incidence of POCD with any of these comparisons.[7] This meta-analysis was limited by the major weakness of all POCD studies which is the difficulty of combining and comparing different studies due to the wide variability in methodological techniques of POCD assessment.

There is a scarcity of research to evaluate the relationship between the duration of anesthesia and POCD. Moller et al. evaluated the duration of anesthesia as a risk factor for POCD in a group of 1218 older patients 60 years and above undergoing major noncardiac surgery at seven days and three months.[8] They compared the difference in POCD incidence when patients were under anesthesia for a duration of 120 minutes or less, 121 – 240 minutes, and 241 minutes or longer.[8] They found that the duration of anesthesia was associated with POCD incidence at seven days (18%, 24%, and 33%, respectively) but not three months after surgery (11%, 9%, and 11%, respectively).[8]

A few studies have evaluated the depth of anesthesia as a risk factor for POCD. Steinmetz et al. studied 70 patients aged 60 years or older who underwent major noncardiac surgery.[3] The depth of anesthesia was monitored using the cerebral state monitor, which provided a cerebral state index (CSI) value.[3] The duration of anesthesia was not different in patients with deep anesthesia (CSI < 40) and light anesthesia (CSI > 60).[3] They were not able to find a significant difference in the incidence of POCD between the two groups at seven days after surgery and they did not do any further follow-up.[3] However, this study was underpowered and there was the possibility of type II error.[3] Farag et al. randomized 74 patients older than 50 years to either a lower Bispectral Index (BIS) anesthesia regimen (median = 39) or a higher BIS regimen (median = 51) during the surgical procedure.[9] Patients' cognitive status was assessed preoperatively and four to six weeks after surgery using a cognitive battery that included tests to measure processing speed, working memory, and verbal memory.[9] Processing speed was the only significantly different test between the two groups with higher processing speed observed in the group with lower BIS or deeper depth of anesthesia. There was no significant difference between the two groups with the other two cognitive tests.[9] Chan et al. randomized patients 60

years or older undergoing any elective major surgery to receive BIS-guided anesthesia or routine care.[10] There was a significant difference between the two groups in depth of anesthesia (BIS median = 53 and 36; $p < 0.001$, respectively).[10] There was no significant difference between the two groups in cognitive function seven days after surgery.[10] However, three months after the surgery, the patients in the BIS-guided group with lighter depth of anesthesia had a lower incidence of POCD compared with the routine care group with deeper level of anesthesia (10.2% vs. 14.7%; adjusted odds ratio (OR) = 0.67; 95% confidence interval (CI) = 0.32 – 0.98; $p = 0.025$).[10] This study suggests that lighter depth of anesthesia is associated with better long-term cognitive outcomes after major surgery.

Royse et al. investigated the influence of propofol or desflurane on the incidence of POCD in a randomized trial of 180 patients undergoing coronary artery bypass surgery (CABG).[11] They found that the incidence of POCD was significantly higher with propofol compared with desflurane when they assessed patients' cognitive function three to seven days after surgery (67.5% vs. 49.4%, respectively; $p = 0.018$).[11] However, there was no difference in the incidence of POCD with propofol compared with desflurane at three months after surgery (11.2% vs. 10.0%, respectively).[11] The results of this study show that propofol may increase the risk of short-term POCD after cardiac surgery. Höcker et al. randomized patients 65 years and older undergoing elective abdominal or urologic surgery to receive anesthesia with sufentanil and either propofol or xenon.[12] Patients' cognitive function was assessed one, six, and thirty days after surgery.[12] The study also showed a high incidence of POCD with the use of propofol during the month following surgery, but the incidence was not significantly different when propofol was compared to xenon (50% vs. 44% at 1 day, 18% vs. 12% at 6 days, and 12% vs. 6% at 30 days, respectively).[12] Kadoi et al. also examined the effect of propofol and fentanyl on increasing the

risk of POCD in a group of 180 older patients after CABG who were randomized to receive either propofol or fentanyl.[13] All patients received 10 mg of diazepam by mouth one hour before anesthesia which was induced by 0.3 mg/kg midazolam, 10 g/kg fentanyl, and 0.2 mg/kg vecuronium.[13] There was no significant difference in POCD at 6 months between the two groups (propofol: 6% vs. fentanyl 7%).[13] The results of these studies make it evident that there is still conflicting information regarding the association between certain anesthetic/sedative agents and the risk of POCD.

2. Home and Perioperative Medications

Home medications are any drugs the patient has been taking prior to admission for surgery. Perioperative medications are any drugs given to the patient once he has been admitted for surgery and until discharge from the post-anesthesia care unit (PACU) after the surgery. The main concern is related to medications with anticholinergic or sedative properties that are particularly known to be associated with negative cognitive outcomes in older patients.[14] The age- and disease-associated changes in brain neurochemistry and the way the brain handles such medications in older patients make them more likely to develop cognitive impairment than younger patients.[14] The hypothesis is that the cumulative harmful effects of home medications along with those medications being administered during surgery in addition to the anesthetic and surgical experience can combine together to insult the brain enough to cause POCD. There is not much research that has been done about the use of anticholinergic or sedative medications and increased risk of POCD. Most of the research done has been about the relationship between these medications and development of POD. However, POD has been associated with POCD and risk factors for POD might play a role in the development of POCD.[15,16] Recent studies have

suggested that the total burden of anticholinergic drugs may determine the development of delirium rather than any single agent.[14] There are several drugs with anticholinergic characteristics that are prescribed with high frequency to patients during and after surgery. Examples of these drugs are antihistamines (H_1-blockers), antidepressants, antipsychotics, antiepileptics, anti-emetics, and muscle relaxants.[17] Tune et al. investigated found a significant association between serum levels of anticholinergic drugs and POD in patients undergoing cardiac surgery.[18] Patients with POD had significantly higher serum level of anticholinergic drugs ($p < 0.001$).[18]

Benzodiazepines (BDZs) is another group of medications that is frequently prescribed in older patients. They are used to manage anxiety and insomnia in the elderly, and even often prescribed to manage depressed older adults.[19] Many older patients are treated with BDZs for prolonged periods, and long-term use of BDZs can accelerate cognitive decline in these patients.[19] Despite these concerns, epidemiologic data indicate that benzodiazepines are among the drugs most commonly prescribed to older adults.[20] Among community-dwelling older adults, 10 – 30% report using a benzodiazepine at any given time, with approximately half of those being long-term users.[20] There are very few studies that investigated the relationship between BDZs and POCD. A study of older patients undergoing cataract surgery found a statistically significant relationship between the amount of nitrazepam administered and memory decline during the first postoperative week.[19]

Another study by Rasmussen et al. hypothesized that diazepam and its active metabolites could be detected in blood after abdominal surgery in 35 patient 60 years and older.[19] They found a POCD incidence of 48.6%, however; the concentration of diazepam or its metabolite desmethyldiazepam was not associated with POCD.[19] Another study investigated the relationship

between POD and duration of BDZs exposure in 328 patients aged 65 to 80 years old who underwent orthopedic surgery.[21] POD occurred in 26% of BDZs users versus 13% in nonusers ($p < 0.01$) and the incidence was significantly different in long-term BDZs users (daily use for > 1 year) than short-term users (daily use for < 1 year) [35% vs. 10%, respectively].[21]

3. Postoperative Medications

Postoperative medications are drugs taken by the patient after discharge from the PACU and until hospital discharge. Most of the medications administered to the patients at this stage are analgesics, especially opioids being the most commonly used medications for postoperative pain. They are usually administered either orally, intravenously by a nurse, or through intravenous patient-controlled analgesia (PCA). There are reports that the potency of opioids is increased in older adults due to their increased peripheral compartment concentration and longer duration of action.[22] Older patients also increased sensitivity to the effects of BDZs and slower metabolism of long-acting agents.[23,24] On the other hand, there is a debate that leaving the patient with inadequate pain control can put the patient at risk of the same outcomes in addition to unnecessary distress, depression, and sleep disturbance.[22] Deterioration in sleep can cause hyperalgesia which worsens sleep further and increases the need for opioids causing a vicious cycle that can have an indirect negative cognitive outcome.[22] Few studies have been conducted to investigate the relationship between different analgesics, their doses, and route of administration and the risk of POCD and POD.

Marcantonio et al. studied the association between psychoactive medications used postoperatively and POD in a case-control study involving 91 patients.[25] They found that POD was significantly associated with postoperative exposure to meperidine (OR = 2.7; 95% CI = 1.3

– 5.5) and to BDZs (OR = 3.0; 95% CI = 1.3 – 6.8).[25] There was no significant difference in the association between meperidine use and POD whether administered via epidural or PCA.[25] They also found that long-acting (OR = 5.4; 95% CI = 1.0 - 29.2 vs. 2.6; 1.1 - 6.5) and higher doses of BDZ (OR = 3.3; 95% CI = 1.0 - 11.0 vs. 2.6; 0.8 - 9.1) were significantly associated with higher risk of POD[25]. They could not find a statistically significant association between POD and either narcotics or anticholinergic drugs.[25] Wang et al. conducted a prospective cohort study of 225 patients 65 years and older undergoing noncardiac surgery and they assessed patients' cognitive function on days one and two after surgery and they found that 13% of patients experienced POCD on day one, 7% on day two, and 15% had POCD on either day one or day two after the surgery.[26] They also found that the only predictive factor for POCD was postoperative analgesia with opioids, and that patients who received postoperative analgesia orally were at significantly lower risk for the development of POCD (OR = 0.22; 95% CI = 0.06 – 0.80).[26] However, this study assessed POCD too soon after surgery when the patients were still recovering from anesthesia and were under the effect of several medications including sedatives and analgesics. There is always the possibility of confusing POCD with POD when assessing POCD too soon after surgery like in this study. It is also more important to determine if POCD persists on the long-term to confirm that it is not just a temporary condition that occurs during hospitalization of the patients then becomes reversible. Vaurio et al. demonstrated a similar association between postoperative use of opioids via PCA and increased risk of POD compared with patients who used opioids orally.[22] These studies show that pain and pain control are important factors to consider after surgery especially in older patients who may be at higher risk, and that more studies are needed to accumulate enough evidence to guide the pain management practices in this population in a way that prevents or minimizes POD and POCD.

B. SURGERY

1. Type of Surgery

POCD research initially focused on cardiac surgery due to its invasiveness and the severity of complications. There was also an assumption that POCD risk may be higher in on-pump versus off-pump CABG. There was lack of interest in studying POCD after noncardiac surgery until Moller et al. conducted the large ISPOCD1 study in a group of 1218 older patients and showed that POCD was found in 25.8% of study patients one week after surgery and in 9.9% at three months.[8] Evered et al. conducted a recent study to determine the association between surgery type and incidence of POCD after procedures involving light sedation, general anesthesia for noncardiac surgery, and general anesthesia for cardiac surgery involving cardiopulmonary bypass.[6] The study included three surgical groups (n = 644) [coronary angiography (CA) under sedation, major noncardiac surgery (total hip joint replacement [THJR] surgery) under general anesthesia, and CABG surgery under general anesthesia) and one non-surgical control group (n = 34).[6] The incidence of POCD one week postoperatively was 17% for THJR surgery and 43% for CABG surgery (adjusted OR = 0.2, 95% CI = 0.1 - 0.4; $p < 0.01$).[6] At three months, the incidence of POCD was 21% for CA under sedation, 16% for THJR surgery, and 16% for CABG surgery.[6] The mean difference in proportions of POCD among groups was 0.00 (-0.07, 0.07) for CABG versus THJR; -0.05 (-0.12, 0.03) for CABG versus CA; and -0.05 (-0.13, 0.03) for THJR versus CA and there were no significant differences among the three groups (adjusted OR = 1.21, 95% CI = 0.94, 1.55; $p = 0.13$). They concluded that the incidence of POCD is independent of the type of surgery.[6] There was no significant difference at three

months after surgery even between major noncardiac surgery and CABG surgery which is hypothesized to be a major risk factor for POCD in cardiac surgery.

2. Intraoperative conditions

There is a hypothesis that certain irregularities in intraoperative conditions may contribute to increasing the risk of POCD. The major four intraoperative variables that have been considered in the literature as potential risk factors for POCD are hyperthermia, hypotension, hypoxemia, and cerebral embolism. The degree and duration of these conditions also may play a role in the severity of POCD.

Moller et al. conducted a study in 736 patients undergoing major noncardiac surgery with general or regional anesthesia to determine if intraoperative monitoring with pulse oximetry to reduce the risk of hypoxemia would decrease the incidence of POCD.[27] They randomized patients to undergo pulse oximetry monitoring (group 1) or not (group 2).[27] There was no significant difference between the two groups in the incidence of POCD when it was assessed one week and three months after surgery.[27] In the ISPOCD1 study, Moller et al. assessed the incidence of POCD in patients who experienced hypoxemia (defined as one or more episodes of oxygen saturation $\leq$ 80% for > 2 minutes) or hypotension (defined as one or more episodes of mean arterial pressure $\leq$ 60% for $\geq$ 30 minutes) one week and three months after surgery.[8] The incidence of POCD was 26% and 11% in patients with hypoxemia and 26% and 9% in patients with hypotension, respectively.[8] However, they could not find a significant association between different degrees and durations of hypoxemia or hypotension and the incidence of POCD after one week or three months.[8] In some surgical procedures that require dry fields or that are associated with substantial blood loss, anesthesia under deliberate hypotensive conditions can be

beneficial to the patient, but it can also result in ischemic injury in nonsurgical regions, such as the brain and heart.[28] William-Russo et al. randomized 235 older adults undergoing total hip replacement with epidural anesthesia to one of two levels of intraoperative mean arterial blood pressure management (45 – 55 mmHg or 55–70 mmHg).[28] There was no significant difference between the two groups in the incidence of POCD one week or four months after surgery.[28] The current few studies in the literature indicate that there is no significant association between hypotensive or hypoxemic conditions and the risk of POCD.

Thromboembolic events may potentially cause cognitive deficits due to ischemic tissue damage.[4] Rodriguez et al. conducted a study in a convenience sample of 37 patients undergoing total knee arthroplasty (TKA) to investigate the relationship between cerebral emboli and the risk of POCD at one week and three months after surgery.[29] Cerebral emboli occurred in 59.5% of study patients and the incidence of POCD was 41% at one week compared to 18% after three months.[29] However, they could not find a significant association between intraoperative cerebral emboli and POCD.[29] Liu et al. tried to test the hypothesis that off-pump CABG surgery is associated with decreased number of cerebral microemboli and the incidence of POCD.[30] They included 227 Chinese patients undergoing CABG surgery (59 on-pump vs. 168 off-pump) and assessed cognitive function one week and three months after surgery.[30] Though, the group with off-pump CABG surgery had a significantly decreased number of cerebral microemboli, there was no significant difference in the incidence of POCD between the two groups either at one week (55.2% vs. 47.0%; $p = 0.283$, respectively) or three months (6.4% vs. 13.1%; $p = 0.214$) after surgery.[30] They also found that neither on-pump surgery nor cerebral microemboli was associated with POCD.[30] The authors acknowledged some of the limitations of this study such as the lack of randomization and potential bias in patient allocation.[30] Also, there was a difference

in the baseline of one of the cognitive tests in favor of the off-pump group.[30] The results of these studies show that there is a need for more research in this area to address these limitations and accumulate enough evidence to answer the question if cerebral embolism may be a risk factor for POCD.

Only a few non-conclusive studies have been published about the relationship between changes in body temperature during surgery especially hyperthermia and the risk of POCD. Plourde et al. randomized 62 patients 40 – 70 years old undergoing cardiac surgery to either cold or warm CPB (28 °C vs. 36 °C, respectively) and they measured their cognitive function seven days postoperatively.[31] Only 54 patients completed the study (cold CPB = 24; warm CPB = 30).[31] There was a significant postoperative deterioration in both surgical groups, but no differences were observed between groups.[31] However, this study was limited by the small sample size, absence of a control group to adjust for learning effects from repeated administration of the neuropsychological tests, and the assessment of POCD at seven days only and not on the long-term.[31] Grigore et al. also hypothesized that hypothermic CPB would decrease the cognitive deterioration after CABG surgery.[32] They recruited 227 patients undergoing elective CABG surgery who were randomized to either normothermic (35.5 – 36.5°C) or hypothermic (28 – 30°C) CPB and they measured cognitive function six weeks after surgery.[32] There was no difference in cognitive outcomes between normothermic and hypothermic groups.[32] Salzar et al. randomized 150 patients over 65 years of age who were scheduled for total knee replacement to receive standard temperature control (covered with a sheet with no active warming) or active warming (infusion of warmed fluids).[33] They could not find any difference between the two groups in the incidence of POCD three months after the surgery (standard care = 14.3%, active warming = 6.5%; p = 0.2440).[33] These studies show that

there is no evidence yet that body temperature during surgery plays a role in determining the incidence of POCD.

3. Neuroinflammation and Brain Injury Biomarkers

There is a hypothesis that perioperative inflammatory response may be a risk factor for POCD in older adults.[34] Neuroinflammatory response can result from brain trauma during surgery.[34] Inflammation during surgery can induce a number of pro-inflammatory cytokines leading to a systemic acute-phase response, 'the illness response'.[4] The key cytokines that may play a role in the inflammatory process during surgery are interleukin-1 (IL-1), tumor-necrosis factor-alpha (TNF-α), IL-6, and IL-8.[34,35] The initial reaction is usually the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues.[34] This then stimulates the production and release of more cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as the acute phase response.[34] Inflammation has been studied in relation to cognitive deficits in healthy young males and the results showed a marked decrease in self-reported level of concentration and cognitive abilities, as well as sleep impairment.[34] A significant correlation has been found among inflammatory markers, C-reactive protein (CRP) and interleukin-1 (IL-1) and neurocognitive decline in cardiac surgery.[4] Worthy of mention is the hypothesis that neuroinflammation is a common mechanism between POCD and Alzheimer's disease (AD) through the activation of microglial cells which have been suggested to be very important for production of inflammatory mediators in response to stressors.[35,36] Blocking perioperative inflammatory response may play an important role in the future in preventing POCD.[34] Only a few studies are available in the literature about the relationship between inflammatory biomarkers and the risk of POCD.

Brain injury markers have also been studied as possible predictors of POCD assuming that POCD can be a manifestation of transient or permanent cerebral injury.[37] The most commonly studied neuronal injury markers in POCD are S-100β protein and neuron-specific enolase (NSE) and the results of these studies are still conflicting. Increased blood levels of NSE and S-100β protein have been found in patients who sustained clinical neurological complications after cardiac surgery.[38] There are few studies that have been conducted to evaluate the relationship between S-100β and NSE elevation and POCD especially after cardiac surgery.

Lili et al. tested the neuroinflammation theory in 80 patients 65 years or older undergoing abdominal surgery who were randomized to receive ulinastatin (a drug widely used to treat acute systemic inflammatory disorders) or to receive regular care in the control group.[39] They measured cognitive function seven days after surgery and they also measured the level of serum IL-6, TNF-alpha, CRP, and S-100β before the surgery, at the end of the surgery, and on postoperative days one to three.[39] They found that significant decline in cognitive function occurred in eight out of the nine cognitive tests they used.[39] The ulinastatin group had a lower incidence of POCD than the control group (2.5% versus 27.5%; $p < 0.05$).[39] In the control group, serum S-100β protein and IL-6 concentrations increased at the end of surgery and on postoperative days one and two and the levels were significantly higher than those in the ulinastatin group ($p < 0.05$). This recent study showed that the neuroinflammation theory might play a role in the development of POCD and showed the potential for anti-inflammatory drugs to protect against POCD in surgery. Also, the study showed that serum elevation of S-100β protein can predict POCD.

4. Postoperative delirium

POD has been generally linked with increased risk of long-term cognitive and functional decline.[15] POD is usually underestimated after surgery and is subjectively evaluated without the use of validated and reliable tools to measure it. There has been much recent interest in studying the potential relationship between experiencing POD and increased risk of long-term POCD. Rudolph et al. studied a group of 1218 subjects 60 years old or above undergoing elective noncardiac surgery and found an association between POD and POCD one week after surgery (adjusted risk ratio 1.6, 95% CI: 1.1–2.1), but there was no association between them three months after surgery.[15] Hudetz et al. conducted a study in male older patients undergoing cardiac surgery and included a nonsurgical control group that is similar in age and education level.[40] They also found that POCD incidence was significantly greater in patients who had POD delirium (89%) compared with those who did not (37%).[40] The odds of developing POCD in patients with POD were 14 times greater than in those who did not have POD.[40]

5. Postoperative Complications

There is a weak hypothesis that postoperative complications particularly infections and respiratory depression may be risk factors for POCD. There are only a few studies that have investigated the relationship between POCD and these factors. In the ISPOCD1 study, Moller et al. found that postoperative infection and respiratory complications were associated with POCD one week after the surgery.[8] Further research is needed to prove or refute this theory. Abildstrom et al. confirmed that postoperative infections (assessed until three months after surgery) were a significant risk factor for POCD one to two years after noncardiac surgery, but they could not find an association between respiratory complications and POCD.[41]

C. PATIENT

1. Age

Age is the least controversial and strongest independent risk factor for POCD particularly when we focus on long-term POCD which is usually assessed at least three months after surgery to prevent any confusion with POD. Current POCD research is mainly conducted in older patients since the risk of POCD is higher in this population. Moller et al. showed that age was associated with both short- and long-term POCD in a group of 1218 older patients aged 60 years or older undergoing major noncardiac surgery.[8] Monk et al. included 1064 patients aged 18 years or older and conducted a stratified analysis by age group and found that age was associated with POCD three months after noncardiac surgery.[2] The incidence of POCD was 5.7% in young, 5.6% in middle-aged, and 12.7% in older patients.[42] The incidence of POCD was significantly higher in older patients compared to their matched controls ($p < 0.001$).[42] Also, Abildstrom et al. confirmed that age was a significant risk factor for POCD one to two years after noncardiac surgery.[41]

2. Cognitive Reserve

Cognitive reserve refers to a patient's ability to buffer the effects of various insults that may occur to the brain during surgery. However, cognitive reserve is subjective and cannot be precisely measured, therefore surrogates of cognitive reserve have been suggested to include education level, occupational attainment, and performance on tests of knowledge.[43] There is evidence that greater educational attainment is associated with a reduced relative risk of developing Alzheimer's disease and this theory is suggested as one of the factors to be considered when discussing the mechanisms and predictors of POCD.[43] This theory suggests that

patients with higher levels of education, as a hypothetical surrogate of cognitive reserve, may have less deterioration in cognitive function than patients with lower education levels when they are exposed to an equivalent insult. The association between lower occupational attainment and incident dementia has also been discussed in a number of studies.[43] In the ISPOCD1 study, Moller et al. found that lower education level was associated with higher incidence of early POCD at seven days after surgery but not with long-term POCD after three months.[8] Monk et al. confirmed this finding and also concluded that years of education was associated with POCD three months after major noncardiac surgery.[42] However, Abildstrom et al. conducted a study in 336 older patients and followed them for one to two years, but could not find a significant relationship between education level and POCD.[41] So, it seems that education level plays a role in modulating the risk of POCD, but the cognitive reserve concept is probably more complex than that and further research of intellectual measurement and its association with POCD is needed.

3. Pre-existing Cognitive Impairment Before Surgery

Another theory of POCD suggests that patients who have pre-existing cognitive impairment before surgery are at higher risk for POCD. This is particularly important to notice in some patients with very mild, sometimes unobserved, forms of cognitive impairment who just get pushed off of the cognitive cliff by the various stressors during surgery, accelerating their cognitive decline and making it more prominent and sometimes permanent. Bekker et al. tested this hypothesis when they retrospectively examined the records of 169 community-dwelling older patients who were divided into two groups: mild cognitive impairment (MCI) and non-MCI groups. Patients with MCI had a greater decline in cognitive function than the non-MCI

group.[44] Silverstein et al. analyzed the data of the ISPOCD1 to determine if there was an association between preoperative cognitive impairment (PCI) and POCD.[45] They found that the incidence of POCD was 19% in patients classified with PCI compared to 26.4% in non-PCI patients one week after surgery ($p = 0.19$).[45] At three months, the incidence of POCD was 15% in patients classified with PCI compared to 9.5% in non-PCI patients ($p = 0.23$).[45] There was no significant association between preoperative cognitive impairment and POCD one week or three months after surgery.[45] The results of these two studies show that the evidence is still conflicting about this theory, and more research is needed to determine if the presence and degree of preoperative cognitive impairment can predict POCD.

4. Genetic Biomarkers

ApoE4 genotype has been implicated as a risk factor for AD, poor outcome after cerebral injury, and accelerated cognitive decline with aging.[46] There are three different ApoE isoforms or alleles (ε2, ε3, ε4). The ApoE4 allele has been associated with increased risk of atherosclerosis and AD.[47] The link between genetic predisposition with the ApoE4 allele and cognitive decline in the aging population is still debatable, since the ApoE4 allele has also been associated with cerebrovascular diseases and atherosclerosis which can contribute to cognitive decline.[47,48]

Lelis et al. conducted a study in 87 older patients undergoing elective CABG surgery who were genotyped for the presence of the ApoE4 allele.[49] They found that 21.8% of study subjects had POCD and carried the ApoE4 allele.[49] They concluded that ApoE4 genotype was significantly associated with early POCD one week after surgery ($p = 0.04$).[49] However, this study was limited by its small sample size, lack of control group to adjust for learning effects, and the use of Mini-Mental State Examination (MMSE) solely to assess cognitive function

which is inappropriate, as MMSE is only used to screen for dementia, and the current recommendation for POCD assessment is to use a rigorous battery of tests that measures several of the following domains: learning and memory, perception and attention, and executive functioning.[50] Silber et al. could not find an association between ApoeE4 and POCD in 282 patients undergoing CABG surgery when POCD was assessed three and twelve months after surgery.[51] The ApoE4 allele was present in 29.4% of total study patients.[51] At three months after surgery, the incidence of POCD in patients with and without the ApoE4 allele was 7.2% vs. 12.6% (p = 0.601), respectively.[51] At twelve months after surgery, the incidence of POCD in patients with and without the ApoE4 allele was 13.3% vs. 11.6% (p = 0.192), respectively.[51] They concluded that POCD was not associated with ApoE4 in patients undergoing CABG surgery.[51] McDonagh et al. conducted a large study in which they recruited 394 patients over age 55 years undergoing elective major noncardiac surgery.[37] They evaluated the incidence of POCD in 350 patients who completed the study and found that the incidence was 54.3% at six weeks after surgery and 46.1% at one year.[37] There was no difference in the incidence between patients with or without the APOE4 allele (56.6 vs. 52.6%; p = 0.58).[37] The research about the relationship between genetic predisposition with the Apoe4 allele and POCD is very promising, however; there is still a need to accumulate enough evidence to confirm this hypothesis.[37]

5. Comorbidities

There is a hypothesis suggesting that certain patient comorbidities, especially endocrine and vascular disorders, can contribute to the risk of POCD. This is particularly important to study in older patients who usually have multiple comorbidities. Kadoi et al. studied 88 patients undergoing elective CABG and they found that the incidence of POCD six months after the

surgery was 27.3%.[52] There was a significant association between POCD and the presence of renal failure (OR = 2.8; 95% CI = 2.4 - 4.3; $p < 0.01$) and diabetes mellitus (OR = 1.8; 95% CI = 1.2 - 2.4; $p < 0.01$) six months after surgery.[52] Hudetz et al. studied the association between POCD and metabolic syndrome in a group of 60 older patients (30 with metabolic syndrome and 30 without it) after elective major noncardiac surgery and 30 nonsurgical controls.[53] There was a significant association between POCD one month after surgery and having the metabolic syndrome. Patients with the metabolic syndrome had higher POCD incidence than those without it (56.7 vs. 26.7%, respectively).[54] There is a dearth of high quality research in this area, but it seems that diabetes and vascular diseases could play a role in the risk of POCD.

II. SUMMARY

The etiology and pathophysiologic mechanisms of POCD are still elusive and POCD is likely a multifactorial condition. There are three major theories in the literature that may explain POCD: medication, surgery, and patient theories. The variables included in the medication theory are type, duration, and depth of anesthesia, the use of highly anticholinergic or sedative agents before, during, or after surgery, and the use of certain types of analgesic drugs especially opioids postoperatively. The surgery theory suggests that factors associated with higher risk of POCD include the type and duration of surgery, undesirable changes in intraoperative conditions especially hyperthermia, hypoxemia, and hypotension, exposure of the brain to inflammation or traumatic injury during surgery, postoperative delirium, and postoperative complications especially infection and respiratory depression. The third theory is focused on the patient and it suggests that factors such as older age, less cognitive reserve, pre-existing cognitive impairment

before surgery, genetic predisposition with the ApoE4 allele, and patients' comorbidities especially vascular and endocrine diseases may be associated with higher risk of POCD.

III. DISCUSSION

There remains a gap in the literature about the incidence and risk factors for POCD in older adults undergoing major noncardiac surgery. Several studies conducted to date did not use enough neuropsychological tests that are sensitive to small changes in cognitive function to evaluate POCD. Though there is a concern about the burden of lengthy cognitive testing on the patient and the time constraints imposed by the clinical environment to conduct such tests, not using enough tests to assess the various domains of cognitive function may result in missing important cognitive deficits. Most of the studies did not evaluate patients' depression and sleep quality status before conducting cognitive tests to ensure they did not negatively affect patients' performance on cognitive tests. Many study designs used a single group of patients and examined the change in their performance over time without inclusion of a control group, which is similar in age and level of education to the surgical group, to adjust for the learning effects that occur from repeated administration of neuropsychological tests. This can underestimate the incidence of POCD since patients may falsely improve on the tests instead of declining. In conclusion, this research area suffers from several methodological issues that need to be addressed. There is also a lack of studies evaluating the risk of POCD associated with inflammatory biomarkers and genetic predisposition with the ApoE4 allele.

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CHAPTER 3: SIGNIFICANCE AND SPECIFIC AIMS

I. SIGNIFICANCE

POCD is not a new phenomenon and many studies have been conducted in this research area. However, the incidence and potential risk factors of POCD are still elusive. This is mainly due to the discrepancy in the definition of POCD in the literature and the use of measurement tools to assess POCD that are not robust. For instance, many studies used the MMSE to determine if patients had POCD, though MMSE is only validated for dementia screening and should not be used as a neuropsychological tool to diagnose POCD. Also, many studies assessed POCD either too early (e.g., one to seven days after surgery) or too late (e.g. one to two years or longer after surgery). It is inappropriate to assess POCD too early in the postoperative period as it usually gets confused with POD and the residual effects of the anesthesia and sedatives being used during the recovery period. Also, assessing POCD too late can result in not being able to capture the diagnosis and progress of POCD in the few months following surgery when functional and cognitive decline can cause frustration to patients and overall decreased quality of life. It is recommended to assess POCD several times after surgery at reasonable intervals (e.g. one, three, six, and twelve months) because waiting too long for the first assessment can also make it difficult to make the case that observed decline is specifically related to the surgery without the interference of other variables such as age-associated memory loss or the progress of underlying dementia.

Only a few studies acknowledged and adjusted for the fact that depression and poor sleep quality can negatively affect patients' performance on neurocognitive tests used for assessment of POCD. Most POCD studies focused on patients undergoing cardiac surgery, particularly on-

pump CABG surgery, and researchers' attention has just recently shifted to studying POCD after major noncardiac surgery. Only a few researchers have investigated the relationship between pre-existing cognitive impairment before surgery and the risk of POCD development. Also, few studies investigated the potential relationship between genetic predisposition with the ApoE4 allele or the release of several pro-inflammatory cytokines produced in response to surgical stressors and the risk of POCD. Also, there are no studies that investigated the relationship between home medications particularly those with highly anticholinergic or sedative effects and the risk of POCD. There is a scarcity of studies about the effect of intraoperative conditions particularly body temperature, blood pressure, and oxygen saturation and the risk of POCD. Lastly but most importantly, many POCD studies did not include a nonsurgical control group to adjust for the learning effects from repeated administration of neuropsychological tests which can falsely underestimate the incidence of POCD.

These gaps and limitations of the current literature were the reasons to conduct our exploratory study that is intended to determine the incidence and explore the largest number of potential risk factors associated with long-term POCD. We used a robust computerized neuropsychological battery that is valid, reliable, and sensitive to subtle changes in cognitive function. The battery can also assess several important cognitive domains while minimizing learning effects by providing alternate forms of the same test, meaning that no two presentations of the same test are ever the same.

The outcomes of this study will help clinicians, patients, and their caregivers make better informed decisions before they undergo major noncardiac surgery. With current advances in surgery and anesthesia, older patients are less hesitant to undergo surgery, particularly noncardiac procedures such as orthopedic or neurosurgery. The study seeks to provide additional

evidence to guide these patients and their care providers in assessing the risk-benefit ratio of undergoing this type of surgery. It may also help healthcare providers to use the least provocative drugs and techniques without losing the benefits of surgery by identifying the risk factors for POCD and if some of them may be modifiable.

II. SPECIFIC AIMS

The specific aims of this study were to:

a. Determine the incidence of POCD in older adults three months after elective major noncardiac surgery.
b. Identify potential risk factors of POCD in older adults three months after elective major noncardiac surgery.

III. SUMMARY

There is a gap in the literature about the incidence and risk factors of POCD in older patients undergoing major noncardiac surgery. The current evidence is either flawed or not sufficient to draw definitive conclusions. The specific aims of our study were to determine the incidence and risk factors of long-term POCD in older adults undergoing major noncardiac surgery. The outcomes of our study should help clinicians, patients, and their care providers make better informed decisions when it comes to undergoing this type of surgery understanding the incidence of POCD and who might be at risk of experiencing cognitive deterioration after surgery.

CHAPTER 4: METHODS

This is a prospective cohort study of patients aged 65 years and older who were undergoing elective major noncardiac surgery at Virginia Commonwealth University Health System (VCUHS). All patients provided written informed consent and the study has been approved by VCU Institutional Review Board (IRB).

I. STUDY POPULATION

Patients were recruited during their visit to the pre-anesthesia clinic at VCUHS. Patients had to be able to communicate in English and have the capacity to sign written informed consent. Patients were excluded from the study if they were scheduled for another major surgery within three months of the study surgery. Patients were also excluded if they scored less than 24 on the MMSE-2 standard version during their initial interview. Patients were excluded if they had a diagnosis or history of psychiatric disorders (e.g., schizophrenia and bipolar disorders), neurodegenerative diseases (e.g., dementia), or metabolic diseases (e.g., diabetes) unless they were under the observed care of a physician for the disorder, were taking their prescribed drug regimen, and they appeared to the investigator team to be without evidence of cognitive problems. Patients were excluded if they had a history of brain tumor or head trauma or if they had any kind of motor dysfunction or physical disability (e.g., Parkinson's disease), or any visual or hearing impairment that would preclude computerized neurocognitive testing.

We also recruited a nonsurgical control group to adjust for the learning effects that may occur from repeated administration of neuropsychological tests. The control group was constituted of subjects aged 65 years or older recruited from an outpatient geriatric clinic at

VCUHS during their regular checkup in addition to eligible individuals who accompanied study patients to the pre-anesthesia clinic before surgery and were willing to serve as study controls. We also included patients who originally joined the study in the patients group, but their surgery was canceled or rescheduled for more than three months later. The control group had the same inclusion and exclusion criteria as the study patients except that they were not having any major surgery scheduled within three months of their involvement in the study.

II. TYPE OF SURGERY AND ANESTHESIA

Each study patient received either general anesthesia (inhaled and/or intravenous), regional anesthesia (epidural, spinal, and/or nerve block) with sedation, or a combination of general and regional anesthesia based on a collaborative decision among surgeons, anesthesia providers and each individual patient as is the current standard practice at VCUHS without any influence from the study investigators.

III. OUTCOME ASSESSMENT

We used a computerized neurocognitive battery called CNS Vital Signs™ (CNSVS) to assess cognitive function in both patients and controls. The assessment of cognitive function using a computerized battery may be uniquely suited to early detection of cognitive changes in the elderly.[2] Computerized neurocognitive batteries have the advantages of covering a wider range of abilities, minimizing floor and ceiling effects, standardizing the test administration, and precisely recording accuracy and speed of response with a level of sensitivity not possible in standard administrations with conventional paper-and-pencil testing.[2] In addition, they are cost- and time-saving compared to conventional neurocognitive tests. They also allow appropriately

trained personnel, other than only a neuropsychologist, to be able to administer these tests as long as the interpretation of the results is done by the appropriate healthcare professional.[2] CNS Vital Signs™ neurocognitive battery has high validity and test-retest reliability, and it has been evaluated in 1069 volunteers with age range of seven to ninety years old who were in good health, without past or present psychiatric or neurological disorders, head injury, learning disabilities, etc.; and were not taking any centrally-acting medications.[3] Five tests were administered to the study patients and controls as described below:

1. The Verbal Memory test is an adaptation of the Rey Auditory Verbal Learning test.[3] Fifteen words are presented, one by one, and each stays on the screen for two seconds. The subject is asked to remember these words, and then a longer list of thirty words is presented that contains the first fifteen words the patients was asked to remember in a randomly mixed manner. When the subject recognizes a word from the original shorter list, he presses the spacebar on the keyboard. After this, the patient continues to complete the remaining tests in the battery and just before the end of the testing session (about 20 minutes later), he is provided with another long list of thirty words that contains the original fifteen words in a randomly mixed manner and he is asked again to recognize the original fifteen words.
2. The Visual Memory which is based on the Rey Visual Design Learning test is exactly the same as the Verbal Memory test except that fifteen and thirty geometric figures are presented to the patient in the original and following lists, respectively, instead of words.
3. The Symbol Digit Coding test is a variant of the Wechsler Digit Symbol Substitution test.[3] The subject is given a training session to be familiar with the test before taking the actual one. The test consists of serial presentations of screens, each of which contains a

bank of eight symbols above and eight empty boxes below.[3] The subject types in the number that corresponds to the symbol that is highlighted.[3] Only the digits from two through nine are used to avoid the confusion between "1" and "I" on the keyboard.[3] This test lasts for 120 seconds and the goal is to type in as many correct numbers as one can in this time frame.[3]

4. The Stroop Color test is a modification of the Stroop Color Word Interference test and it has three parts.[3] In the first part, the words RED, YELLOW, BLUE, and GREEN (all printed in black) appear at random on the screen, and the subject presses the spacebar as soon as he sees the word which generates a simple reaction time score.[3] In the second part, the words RED, YELLOW, BLUE and GREEN appear on the screen but printed in color and the subject is asked to press the spacebar when the color of the word matches what the word says.[3] In the third part, the words RED, YELLOW, BLUE and GREEN appear on the screen, printed in color and the subject is asked to press the spacebar when the color of the word does not match what the word says.[3]
5. The Shifting-Attention test is based on Trails B and Wisconsin Card Sort test.[3] Subjects are instructed to match geometric objects either by shape or color.[3] Three figures appear on the screen, one on the top and two on the bottom.[3] The top figure is either a square or a circle and the bottom figures are a square and a circle.[3] The figures are either red or blue; the colors are mixed randomly and the subject is asked to match one of the bottom figures to the top figure using a rule that is stated at the top and that keeps randomly changing at each presentation (e.g., sometimes it will say 'match color' or 'match' shape in other times).[3] This goes on for 90 seconds and the goal is to make as many correct matches as one can in the time allotted.[3]

The tests embrace an appropriate span of cognitive domains (composite memory, processing speed, executive function, reaction time, and cognitive flexibility) and have been shown to be sensitive to most of the causes of mild cognitive impairment.[3] The testing time required to complete this battery is about 30 minutes. Because the presentation of stimuli in this battery is randomized, no two presentations of a specific test are ever the same, making the battery appropriate for repeated administration with minimal learning effect. Also, the battery provides a brief practice before each test, except for the verbal and visual memory tests, to make patients familiar and comfortable with test administration. The personnel who administered the battery were extensively trained on neuropsychological test administration and relevant interview techniques. Cognitive testing was conducted in a very quiet place and with no distractions to the patient at all for the duration of the test. Patients were allowed to take breaks between the tests if they felt exhausted, and to ask clarifying questions at any time.

We compared the level of computer use familiarity between the patient and control groups to make sure it did not affect their performance differently on neurocognitive tests. We asked subjects in both groups to self-rate their familiarity with general computer use as not familiar at all, little familiar, familiar, very familiar, or expert with computer use. We then categorized subjects into three groups (not familiar at all, little familiar/familiar, very familiar/expert) for the purpose of statistical analysis.

Patients' cognitive function was assessed preoperatively and three months after postoperatively. We allowed flexibility of two weeks within which cognitive testing had to be conducted in order to accommodate for patients' schedules. Preoperative assessment of cognitive function was conducted during patients' visit to the pre-anesthesia clinic. Postoperative assessment of cognitive function was conducted either at the hospital if patients had a follow-up

visits three months after surgery, or at patients' residence if they did not have a follow-up visit three months after surgery and they were not willing to come to the hospital for follow-up. The same neurocognitive battery was used to assess cognitive function in the study controls at baseline (time of recruitment) and three months later allowing flexibility of two weeks within which cognitive testing had to be conducted in order to accommodate for controls' schedules. Baseline assessment of cognitive function was conducted during controls' visit to the outpatient geriatric clinic at VCUHS, or at the pre-anesthesia clinic if the control was accompanying a study patient. The follow-up testing at three months was conducted either at the hospital or residence of the subjects in the control group if they were not willing to come to the hospital for follow-up testing.

IV. ASSESSMENT OF POSTOPERATIVE DELIRIUM (POD)

We evaluated study patients for the presence of POD 48 hours after their surgery while they were still in the hospital. Our goal was to determine if patients who experienced POD after postoperatively were more likely to experience POCD three months after surgery. We used the Confusion Assessment Method (CAM) for this purpose.[4] This test has been validated and it has high sensitivity (94 – 100%) and specificity (90 – 95%) for detection of delirium.[4] It is also relatively easy and quick to administer, as it takes only five to ten minutes to complete.

V. DEPRESSION AND SLEEP QUALITY TESTING

It is well known that several factors including depression and poor sleep quality may have a negative impact on a subject's motivation, and can adversely affect his performance on neuropsychological tests.[5,6] For this reason, we evaluated our study subjects for the possibility of

having depression and poor sleep quality before each cognitive testing session using the Geriatric Depression Scale - Short-Form (GDS-SF) and the Pittsburgh Sleep Quality Index (PSQI), respectively. The GDS-SF is composed of 15 yes/no questions and it has been compared to the long-form 30 yes/no questions and showed to have equivalent sensitivity and specificity in older adults.[7] A score of 5 - 10 on the GDS-SF is suggestive of mild depression and a score of 11 - 15 is suggestive of severe depression. The PSQI takes about five minutes to administer and provides a highly valid, reliable, and standardized measure of sleep quality for the previous month.[8] It also provides an index that is easy for researchers and clinicians to interpret and compare among different patients.[8] In patients with primary insomnia, PSQI has shown a test-retest reliability of 0.87, sensitivity of 89.6 – 98.7, and specificity of 84.4 – 86.5.[8,9] A score of more than five on the PSQI is suggestive of poor sleep quality, and the higher the score, the poorer patient's sleep quality is.

Our goal was to make sure we are only evaluating the change in cognitive function before and three months after surgery in the surgical group with minimal or no interference from other factors that could affect performance of study subjects on cognitive tests. First, we tested if there was any significant change in the depression and sleep quality test scores from baseline till follow-up within each study group, which could affect the performance of any of the two groups differently on neurocognitive tests. Second, we compared the depression and sleep quality test scores between the patient and control groups at baseline and follow-up to determine if there was a difference between the two groups in depression status or sleep quality that could affect their performance differently on neurocognitive tests.

VI. DATA COLLECTION

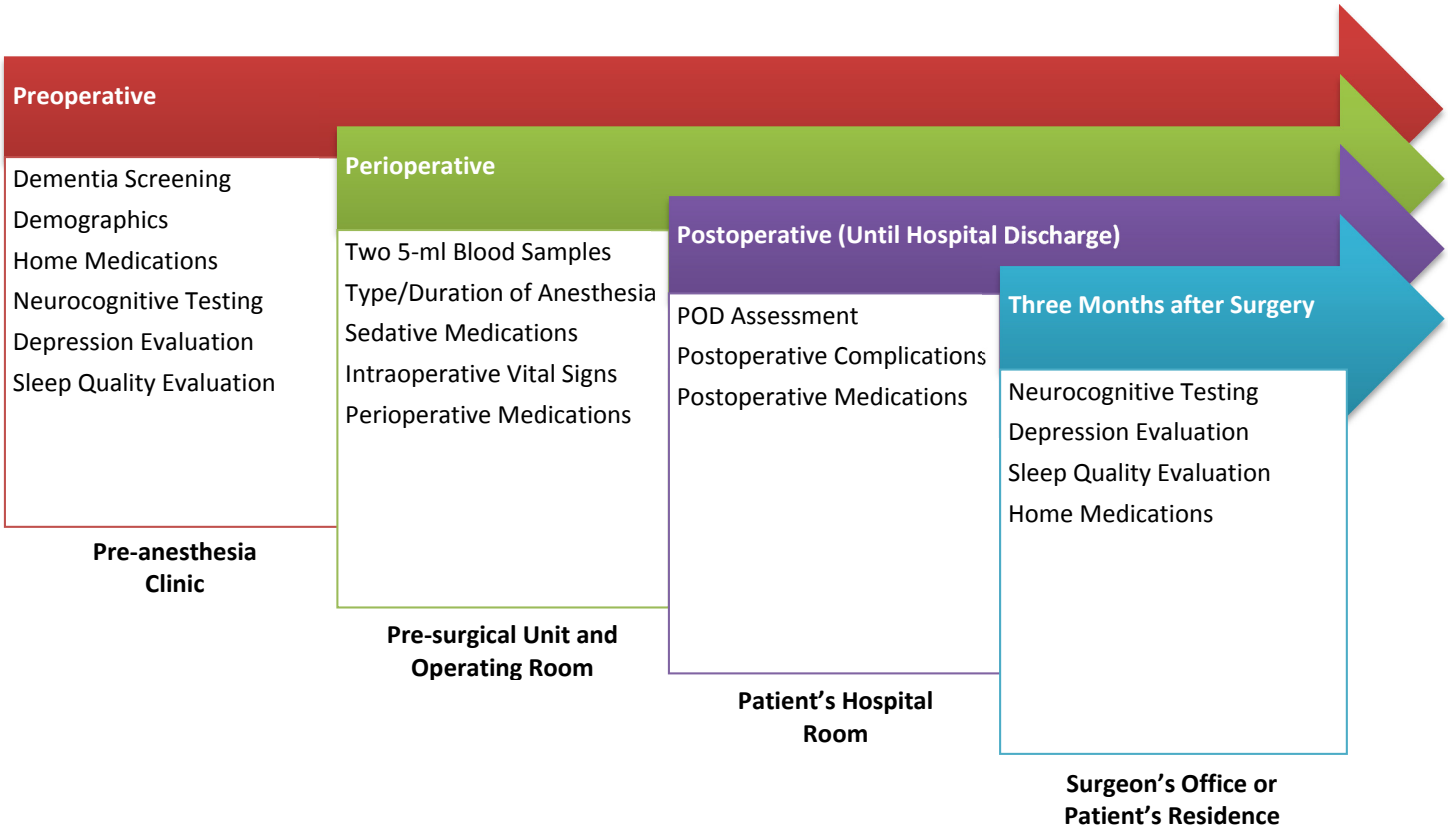
Patients' demographics, medical history, medication use, level of education, and computer familiarity were documented before surgery by questioning the patients and reviewing their medical charts. During the surgery, we collected information about the type, and duration of anesthesia used. We also documented the type of surgery and the incidence of intraoperative hypothermia, hypotension, and hypoxemia. For the purpose of this study, based on the views of the anesthesia clinicians and surgeons involved in the study, we operationalized the definitions of hypothermic, hypotensive, and hypoxemic events. A hypotensive event was defined as mean blood pressure that is 20% lower than baseline. A hypothermic event was defined as body temperature equal to or less than 36 ºC. A hypoxemic events was defined as oxygen saturation less than 90%. After the surgery, we documented all postoperative medications taken by the patient and any complications the patient may have experienced until hospital discharge. Study data were collected and managed using the Research Electronic Data Capture (REDCap™) tool hosted at VCU.[1] REDCap™ is a secure, web-based application designed to support data capture for research studies. Figure 1 summarizes the data collection process throughout the study from baseline to follow-up.

VII. APOE GENOTYPING

On the day of surgery, we collected a 5-ml blood sample in a purple-top vacutainer just before the induction of anesthesia from patients who opted to do this optional part of the study. The sample was stored at -80 ºC until DNA purification has been done using the Spin-Column protocol (DNeasy® Blood Kit, QIAGEN®). A 10 µl of diluted DNA per sample was transferred into a 96-well plate. The DNA plate was placed into a thermal cycler and heated to 95 ºC for 5

minutes. Once the heating process was completed, the DNA plate was placed on ice. DNA amplification was performed using Taq polymerase kit (cat no. 18038-240, Invitrogen™). The PCR product was checked on a 1% agarose gel electrophoresis. Restriction length fragment polymorphism digestion was done by Hhal restriction enzyme. At the end of the incubation, the reactions were terminated by the addition of bromophenol blue dye. The samples were then loaded onto polyacrylamide gels. DNA ladder was added as reference and electrophoresis was run. The gel was then soaked in a solution of ethidium bromide and viewed under UV light. A computer-generated picture of the gel was recorded. Two independent researchers reviewed the gel images and assigned an APOE genotype based on appropriate banding.

Figure 1. Summary of Data Collection Process from Baseline to Follow-up



VIII. INFLAMMATORY BIOMARKER ANALYSIS

On the day of surgery, we collected a 5-ml blood sample in a gold-top vacutainer just before the induction of anesthesia from patients, who opted to do this optional part of the study, to determine the preoperative level of CRP and evaluate if patients with preoperative heightened inflammatory response may be at higher risk for POCD. The blood sample was allowed to clot for 30 minutes after collection then it was centrifuged at 3500 RPM for 10 minutes at 4 ºC. The CRP analysis was done on the serum using the polyethylene glycol (PEG) enhanced immunoturbidimetric assay on Advia® 1800 analyzer.[10] The method uses PEG to accelerate the antigen-antibody interaction. The sample was allowed to react with a specific antiserum to form a precipitate that was measured turbidimetrically at 340/694 nm. By constructing a standard curve from the absorbances of standards, concentrations were determined. The reference range for CRP level is 0.0 – 0.5 mg/dL and any value above that was considered high. The limit of quantification for the test was 0.3 – 32.0 mg/dL. Estimates of precision, based on Clinical and Laboratory Standards Institute (CLSI) recommendations, are consistent with typical performance. The within run precision is less than 5% coefficient of variation (CV) and the standard deviation (SD) is equal to or less than 1, and the total precision is less than 5% CV and SD is equal to or less than 1.

IX. STATISTICAL ANALYSIS

Descriptive analysis of patients' demographics, education level, computer familiarity, and baseline MMSE-2 score was conducted. Continuous data were reported as mean and standard deviation and/or range, and were compared using *t*-test or analysis of variance (ANOVA).

Proportions were given as numbers and percentages were compared using Chi-square (χ^2) or Fischer's exact test, when applicable.

The scores of GDS-SF and PSQI were compared at baseline and three months later within each of the patient and control groups using paired *t*-test to determine if there has been any significant change in depression status or sleep quality from baseline to follow-up that could have affected their performance differently on cognitive tests. Next, the scores of depression and sleep quality tests were compared between the two groups at baseline and follow-up using ANOVA to determine if there was a significant difference between the two groups in their at baseline or follow-up that could have interfered with their performance on cognitive tests.

A. Specific Aim #1

Determination of the incidence of POCD was done using the *Z*-Score method that was originally used in both the ISPOCD1 and ISPOCD2 studies.[11,12] A nonsurgical control group, that is similar to the patients' group in age, education level, and computer familiarity, was recruited to adjust for potential learning or practice effects that may occur from repeated administration of the cognitive tests. An individual *Z*-score was calculated for each test for each subject in the surgical group by subtracting the mean score change for each test in the control group from the score change in each patient in the surgical group from baseline to follow-up. The result was then divided by the standard deviation for the mean score change in the control group. A composite *Z*-score was also calculated by adding all individual *Z*-scores and dividing them by the standard deviation of the mean sum of *Z*-scores in the control group. A patient was classified as having POCD if he had an individual *Z*-score of less than -1.96 in two or more cognitive tests or a composite *Z*-score of less than -1.96. This technique identifies patients with POCD by

comparing the changes in test scores of an individual patient undergoing surgery with changes in the test scores of the comparable control group over the same time interval.[13]

B. Specific Aim #2

A series of univariable logistic regression analyses using Chi-square were conducted at a less conservative significance level of 0.25 to allow for the selection of potential predictors of POCD without risking excluding some important variables that might play a role in the risk of POCD in the final model. The univariable analysis included potential predictors of POCD from the patient, surgery, and medication theories. The patient variables included age (65 – 74 years old, 75 or older), gender (male, female), race (White, African-American or other), education level (high school or less, more than high school), computer familiarity (not familiar at all, little familiar or familiar, very familiar or expert), vascular and endocrine comorbidities (diabetes, hypertension, hypothyroidism, hypercholesterolemia), and ApoE genotype (ApoE4, non-ApoE4). The surgical variables included type of surgery (orthopedic surgery, neurosurgery), type of anesthesia [general (inhaled, intravenous), regional (epidural, spinal, nerve block), a combination of general and regional], duration of anesthesia (less than three hours, three hours or more), use of nitrous oxide for general anesthesia (yes, no), use of desflurane for general anesthesia (yes, no), use of sevoflurane for general anesthesia (yes, no), preoperative level of CRP (normal or low, high), postoperative delirium (yes, no), hypotensive events (yes, no), hypoxemic events (yes, no), and hypothermic events (yes, no). The medication variables included the use of highly anticholinergic or sedative-hypnotic medications at home and postoperatively (nonusers, users of one or more medications). The medication selection was based on potential cognitive adverse outcomes of these medications in older adults as

documented in the American Geriatrics Society 2012 updated Beers criteria for potentially inappropriate medication use in older adults.[14] We also evaluated the use of morphine (IV and PCA), hydromorphone (IV and PCA), and oxycodone as postoperative analgesics (users, nonusers) to determine if they were risk factors for POCD.

The model building process was done using backward stepwise logistic regression (*p*-value was set at 0.25 and 0.10 for entering and leaving the model, respectively). The use of backward stepwise regression was preferred due to the exploratory nature of our study and the lack of definite knowledge of the potential predictors of POCD. Backward stepwise regression begins with a model that includes all potential candidate variables of interest and minimizes the risk of an important predictor not entering the model if the forward selection method was used. Starting with all predictors, backward stepwise has the opportunity to identify and account for any suppressor relationship among variables that can be found in the data. However, the backward stepwise method has the disadvantage that it capitalizes on chance and the presence of a large number of variables at once can lead to too many comparisons that may increase the risk of 'noise' variables being included, which can decrease the predictive power of the model.

Results of the logistic regression analysis were reported as adjusted OR and 95% CI for each variable in the multivariable logistic model using Firth's method to accommodate for the rarity of outcome and small sample size in our study. In normal logistic regression using the maximum likelihood estimation method, we need at least five to ten events/outcomes in the group with the smaller number of events for each predictor to be tested in the model. Firth' method uses penalized maximum likelihood estimation method to reduce biased estimation in case of rare events like in our study allowing us to relax the criteria of five to ten events per tested predictor. We considered p-values less than 0.05 to be statistically significant, and p-

values were two-sided for all statistical tests, when applicable. Data analysis was performed using JMP® Pro 10.0.2 (SAS® Institute Inc., Cary, NC).

X. REFERENCES

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CHAPTER 5: RESULTS

I. DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF STUDY SUBJECTS

A total of 130 patients (surgical group) and 103 controls (nonsurgical group) were approached for possible inclusion in the study, from which 96 patients and 93 controls consented to participate in the study. After applying the inclusion and exclusion criteria and eliminating those who were lost to follow-up, a total of 69 surgical and 54 nonsurgical were included in the study and final analysis. Figures 1 and 2 show the recruitment process for the surgical and nonsurgical groups, respectively.

The mean age for the surgical group was 71 years old and it ranged from 65 – 88 years old. The mean age for the nonsurgical group was 73 years old and it ranged from 65 – 92. There was a marginal difference between the two groups in age ($p = 0.0428$). White patients constituted 81.2% of the surgical group and 14.5% were African-American. In the nonsurgical group, 51.9% were White and 48.1% were African-American. There was a difference between the two groups in race ($p < 0.0001$). Females constituted 66.7% in the surgical group compared to 64.8% in the nonsurgical group. There was no difference between the two groups in gender ($p = 0.8298$). The two groups had similar education level ($p = 0.1085$), and most of the subjects in both groups had an education level above high school (78.3% of surgical and 64.8% of nonsurgical study subjects). There was no difference between the two groups in computer familiarity ($p = 0.6821$). There was also no difference between the two groups in their baseline MMSE-2 score ($p = 0.1235$). Table 1 summarizes the demographics and baseline characteristics of both surgical and nonsurgical groups.

Figure 1. Recruitment Process for the Study Surgical Group

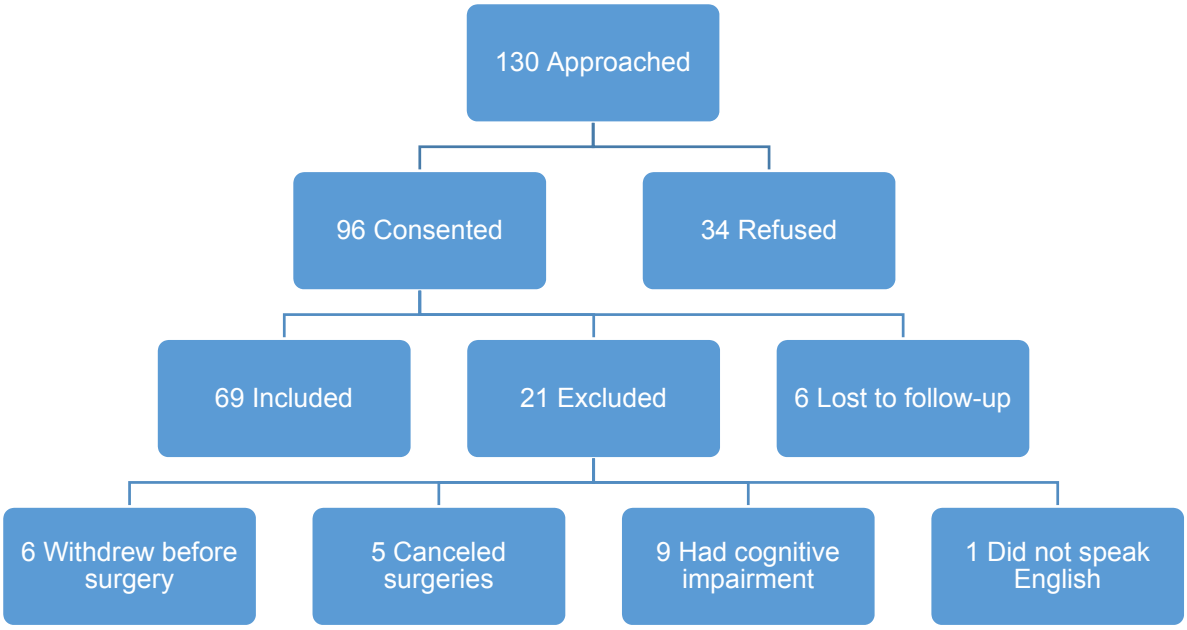

Figure 2. Recruitment Process for the Study Nonsurgical Group

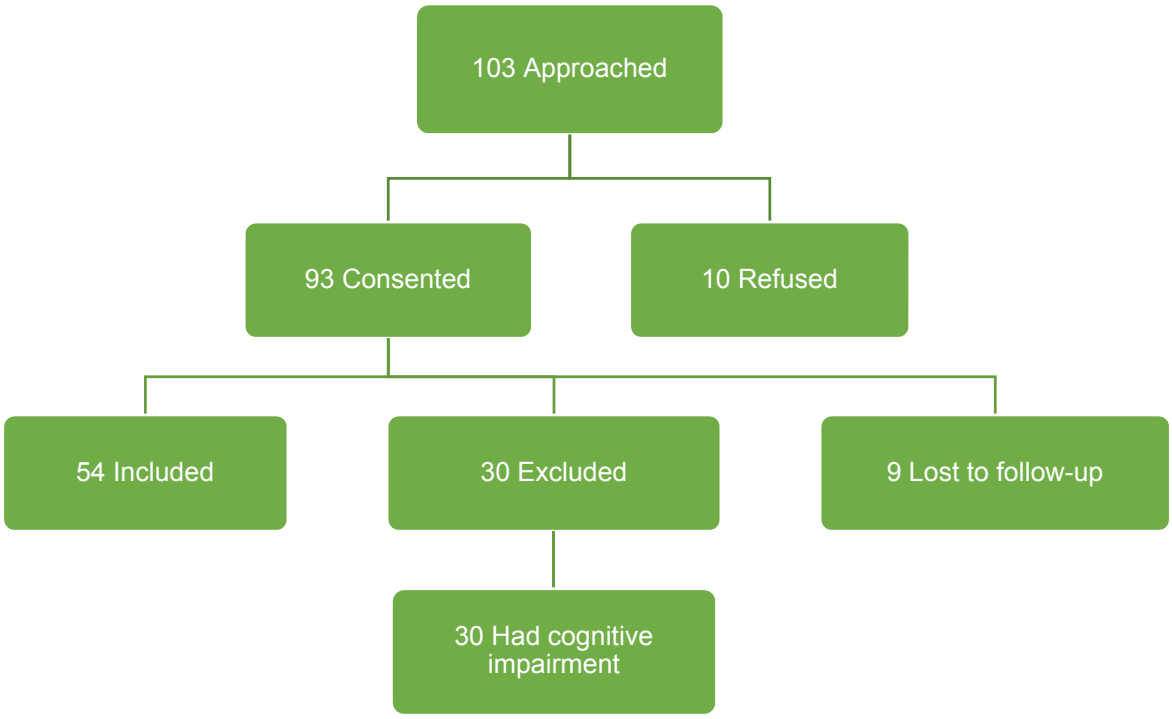

Table 1. Demographics and Baseline Characteristics of Surgical and Nonsurgical Groups

Variable	Surgical (N = 69)	Nonsurgical (N = 54)	*p*-value
Age ± SD (range)	71 ± 5.4 (65 - 88)	73 ± 6.3 (65 - 92)	0.0428*
Gender (Females), %	46 (66.7%)	35 (64.8%)	0.8298
Race, %			<0.0001*
White	56 (81.2%)	28 (51.9%)	
African-American	10 (14.5%)	26 (48.1%)	
Other	3 (4.3%)	0 (0.0%)	
Education Level, %			0.1085
High school or less	15 (21.7%)	19 (35.2%)	
More than high school	54 (78.3%)	35 (64.8%)	
Computer Familiarity, %			0.6821
Not familiar at all	9 (13%)	10 (18.5%)	
Little familiar or familiar	37 (53.6%)	26 (48.1%)	
Very familiar or expert	23 (33.3%)	18 (33.3%)	
MMSE-2 Score ± SD	28 ± 1.4	28 ± 1.7	0.1235

*p-value < 0.05

II. DEPRESSION STATUS AND SLEEP QUALITY AT BASELINE AND FOLLOW-UP

First, we compared the depression status and sleep quality score change from baseline to follow-up within each of the surgical and nonsurgical groups using paired *t*-test to determine if there has been any change in depression or sleep quality within each group from baseline to follow-up. We wanted to rule out the possibility that a change in depression status or sleep quality within any of the two groups could have affected that group's performance on neurocognitive tests differently from baseline to follow-up. Table 2 summarizes the mean and follow-up depression scores and the differences in these scores between the two testing sessions within each group. There was no difference in depression status between the two testing sessions within the surgical or nonsurgical group ($t = 0.67$, $p = 0.51$; $t = -0.99$, $p = 0.33$, respectively). Table 3 summarizes the mean and follow-up sleep quality scores and the differences experienced in these scores from baseline to follow-up within each group. There was no difference in sleep quality from baseline to follow-up within the surgical or nonsurgical group ($t = 0.57$, $p = 0.57$; $t = 0.21$, $p = 0.83$, respectively). These results show that there was no significant change in depression status or sleep quality within the surgical or nonsurgical groups that could have affected their performance on cognitive testing at baseline and the three-month follow-up.

Table 2. Comparison of Depression Status scores within Surgical and Nonsurgical Groups at Baseline and Three-Month Follow-up as Measured by GDS-SF

Group	Time	N	Mean Score	SD	Lower 95% CI	Upper 95% CI
Surgical	Baseline	69	2.1	2.2	1.5	2.6
	Follow-up	69	2.2	2.6	1.6	2.8
	Difference	69	0.1	1.8	-0.3	0.6
Nonsurgical	Baseline	54	2.6	2.7	1.9	3.3
	Follow-up	54	2.3	2.9	1.5	3.1
	Difference	54	-0.3	2.2	-0.9	0.3

Table 3. Comparison of Sleep Quality within Surgical and Nonsurgical Groups at Baseline and Three-Month Follow-up as Measured by PSQI

Group	Time	N	Mean Score	SD	Lower 95% CI	Upper 95% CI
Surgical	Baseline	69	6.8	3.7	5.9	7.7
	Follow-up	69	7.0	3.8	6.1	7.9
	Difference	69	0.2	3.0	-0.5	0.9
Nonsurgical	Baseline	54	6.3	4.0	5.2	7.4
	Follow-up	54	6.4	3.9	5.3	7.4
	Difference	54	0.1	2.6	-0.6	0.8

Second, we compared depression status and sleep quality scores between the surgical and nonsurgical groups at baseline and follow-up using ANOVA to determine if they were different in depression status or sleep quality at baseline or follow-up. Table 4 summarizes the mean GDS-SF scores for both the surgical and nonsurgical groups at baseline and follow-up. ANOVA test showed no difference in depression status between the two groups at baseline ($F(1, 121) = 1.37$, $p = 0.2447$) or after three months ($F(1, 121) = 0.03$, $p = 0.8738$). Table 5 summarizes the mean PSQI scores for both the surgical and nonsurgical groups at baseline and follow-up. ANOVA test showed no difference in sleep quality scores between the two groups at baseline ($F(1, 121) = 0.45$, $p = 0.5059$) or after three months ($F(1, 121) = 0.73$, $p = 0.3954$). These results show that there was no significant difference in depression status or sleep quality between the surgical or nonsurgical groups at either baseline or follow-up that could have affected their performance differently on cognitive testing.

Table 4. Comparison of Depression Status between Surgical and Nonsurgical at Baseline and Follow-up as Measured by GDS-SF

Time	Group	N	Mean Score	SD	Lower 95% CI	Upper 95% CI
Baseline	Surgical	69	2.1	2.2	1.5	2.7
	Nonsurgical	54	2.6	2.7	1.9	3.3
Follow-up	Surgical	69	2.2	2.6	1.6	2.9
	Nonsurgical	54	2.3	2.9	1.6	3.0

Table 5. Comparison of Sleep Quality between Surgical and Nonsurgical at Baseline and Follow-up as Measured by PSQI

Time	Group	N	Mean Score	SD	Lower 95% CI	Upper 95% CI
Baseline	Surgical	69	6.8	3.7	5.9	7.7
	Nonsurgical	54	6.3	4.0	5.3	7.4
Follow-up	Surgical	69	7.0	3.8	6.1	7.9
	Nonsurgical	54	6.4	3.9	5.4	7.4

III. INCIDENCE AND RISK FACTORS OF POCD

A patient in the surgical group was classified as having POCD if he had an individual *Z*-score of less than -1.96 in two or more of the cognitive tests, or a composite *Z*-score of less than -1.96. Based on this method, a total of 11 (15.9%) patients in the surgical group were classified as having POCD. We evaluated the association between POCD and several variables at a preset significance level of 0.25 to screen for potential predictors of POCD to be entered into the final logistic regression model with a significance level of 0.05. We chose the stepwise backward logistic regression method to build the model due to the exploratory nature of this study and lack of a specific hypothesis. Table 6 shows the results of the univariable analysis of potential risk factors for POCD and the distribution of patients with POCD across the levels of each predictor.

Only one patient did not opt to provide blood samples for the purpose of CRP and ApoE4 analysis, which was an optional part of the study that patients could opt out of it. Among the patients who were using anticholinergic drugs before surgery, four were using diphenhydramine, four were using loratadine, three were using meclizine, two were using promethazine, one was using cyclobenzaprine, one was using methocarbamol, one was using tizanidine, one was using solifenacin, and one was using scopolamine. Among the patients who were using sedative-hypnotic drugs before surgery, six were using zolpidem, three were using clonazepam, two were using diazepam, two were using alprazolam, one was using lorazepam, and one was using flurazepam.

In the surgical group, 13 patients received general anesthesia and 48 received regional anesthesia, and eight patients received combined general and regional anesthesia. Among those who received general anesthesia, 20 patients received sevoflurane, two patients received sevoflurane, and seven patients received nitrous oxide.

Table 6. Results of Univariable Analysis for Initial Screening of Potential Risk Factors for POCD

Variable	N = 69	POCD	No POCD	*p*-value
Age				
65 – 74 years old	55	10 (18.2%)	45 (81.8%)	0.4397
≥ 75 years old	14	1 (7.1%)	1 (92.9%)	
Gender				
Male	23	2 (8.7%)	21 (91.3%)	0.3139
Female	46	9 (19.6%)	37 (80.4%)	
Race				
White	56	9 (16.1%)	47 (83.9%)	1.000
African-American or other	13	2 (15.4%)	11 (84.6%)	
Education Level				
High school or less	15	4 (26.7%)	11 (7.3%)	0.2374
More than high school	54	7 (13.0%)	47 (87.0%)	
Computer Familiarity				
Not familiar at all	9	1 (11.1%)	8 (88.9%)	1.000
Little familiar or familiar	37	6 (16.2%)	31 (83.8%)	
Very familiar or expert	23	4 (17.4%)	19 (82.6%)	
Diabetes				
No	57	9 (15.8%)	48 (84.2%)	1.000
Yes	12	2 (16.7%)	10 (83.3%)	
Hypertension				
No	31	6 (19.4%)	25 (80.6%)	0.5251
Yes	38	5 (13.2%)	33 (86.8%)	
Hypothyroidism				
No	64	10 (15.6%)	54 (84.4%)	1.000
Yes	5	1 (20.0%)	4 (80.0%)	

Hypercholesterolemia				
No	57	9 (15.8%)	48 (84.2%)	1.000
Yes	12	2 (16.7%)	10 (83.3%)	
ApoE4 Genotype#				
Non-ApoE4	54	6 (11.1%)	48 (88.9%)	0.0407
ApoE4	14	5 (35.7%)	9 (64.3%)	
Type of Surgery				
Orthopedic Surgery	61	8 (13.1%)	53 (86.9%)	0.1090
Neurosurgery	8	3 (37.5%)	5 (62.5%)	
Type of Anesthesia				
General anesthesia	13	3 (23.1%)	10 (76.9%)	0.0091
Regional anesthesia	48	4 (8.3%)	44 (91.7%)	
Combined general and regional anesthesia	8	4 (50.0%)	4 (50.0%)	
Duration of Anesthesia				
Less than three hours	23	6 (26.1%)	17 (73.9%)	0.1611
Three or more hours	46	5 (10.9%)	41 (89.1%)	
Use of Nitrous Oxide for General Anesthesia				
No	62	8 (12.9%)	54 (87.1%)	0.0751
Yes	7	3 (42.9%)	4 (57.1%)	
Use of Desflurane for General Anesthesia				
No	67	10 (14.9%)	57 (85.1%)	0.2954
Yes	2	1 (50.0%)	1 (50.0%)	
Use of Sevoflurane for General Anesthesia				
No	49	5 (10.2%)	44 (89.8%)	0.0669
Yes	20	6 (30.0%)	14 (70.0%)	
CRP Level#				
Normal or low	50	7 (14.0%)	43 (86.0%)	0.7175
High	18	3 (16.7%)	15 (83.3%)	

Postoperative Delirium^				
No	44	5 (11.4%)	39 (88.6%)	0.6014
Yes	10	2 (20.0%)	8 (80.0%)	
Hypotensive Events				
No	7	1 (14.3%)	6 (85.7%)	1.000
Yes	62	10 (16.1%)	52 (83.9%)	
Hypoxemic Events				
No	63	11 (17.5%)	52 (82.5%)	0.5795
Yes	6	0 (0.0%)	6 (100.0%)	
Hypothermic Events				
No	10	3 (30.0%)	7 (70.0%)	0.1920
Yes	59	8 (13.6%)	51 (86.4%)	
Use of ≥ 1 Anticholinergic or Sedative-Hypnotic				
Drugs at Home Prior to Surgery				
Nonusers	44	4 (9.1%)	40 (90.9%)	0.0830
Users	25	7 (28.0%)	18 (72.0%)	
Use of ≥ 1 Anticholinergic or Sedative-Hypnotic				
Drugs after Surgery				
Nonusers	37	4 (10.8%)	33 (89.2%)	0.2106
Users	32	7 (21.9%)	25 (78.1%)	
Use of Morphine for Postoperative Pain				
No	66	9 (13.6%)	57 (86.4%)	0.0640
Yes	3	2 (66.7%)	1 (33.7%)	
Use of Hydromorphone for Postoperative Pain				
No	29	5 (17.2%)	24 (82.8%)	1.000
Yes	40	6 (15.0%)	34 (85.0%)	
Use of Oxycodone for Postoperative Pain				
No	14	3 (21.4%)	11 (78.6%)	0.6827

Yes	55	8 (14.6%)	47 (85.4%)

*p-value < 0.25

#One patient refused to provide blood samples for testing of genetic and inflammatory biomarkers

^Fifteen patients were discharged earlier than the time for assessment of postoperative delirium

The variables that were included in the final model were ApoE4 genotype, use of one or more highly anticholinergic or sedative-hypnotic medications at home, and the use of sevoflurane for anesthesia. There was no evidence of lack of fit of the final model for the included variables which was tested using Hosmer-Lemeshow goodness-of-fit test (p = 0.9550). Table 6 presents the results of the multivariable logistic regression analysis with adjusted OR, 95% CI, and p-values for the predictors that were entered in the final model and also the incidence of POCD at different levels of each variable.

The association of ApoE4 genotype with POCD was such that patients in the surgical group who had the ApoE4 gene were more likely to have POCD three months after the surgery as compared to patients who did not have the ApoE4 gene (OR = 4.74, 95% CI = 1.09 – 22.19, p = 0.0371). Patients in the surgical group who were using one or more highly anticholinergic or sedative-hypnotic drugs at home before surgery were more likely to have POCD three months after the surgery when compared to patients who were not taking any drug with high anticholinergic or sedative-hypnotic characteristics (OR = 5.64, 95% CI = 1.35 – 30.22, p = 0.0137). Patients who were administered sevoflurane for anesthesia were more likely to have POCD three months after surgery than patients who did not receive it (OR = 6.43, 95% CI = 1.49 – 34.66, p = 0.0102).

Table 7. Results of Multivariable Logistic Regression showing Factors Associated with POCD

Variable	N	POCD	No POCD	Adjusted OR (95% CI)	*p*-value
ApoE4 Genotype					
Non-ApoE4	54	6 (11.1%)	48 (88.9%)	1.00	0.0371*
ApoE4	14	5 (35.7%)	9 (64.3%)	4.74 (1.09 – 22.19)	
Use of ≥ 1 Anticholinergic/Sedative-Hypnotic Drugs at Home Prior to Surgery					
Nonusers	44	4 (9.1%)	40 (90.9%)	1.00	0.0137*
Users	25	7 (28.0%)	18 (72.0%)	5.64 (1.35 – 30.22)	
Use of Sevoflurane for Anesthesia					
No	49	5 (10.2%)	44 (89.8%)	1.00	0.0102*
Yes	20	6 (30.0%)	14 (70.0%)	6.43 (1.49 – 34.66)	

*p-value < 0.05

IV. SUMMARY

The study included 69 patients aged 65 years and older who underwent elective major noncardiac surgery (orthopedic surgery and neurosurgery) and 54 nonsurgical controls to adjust for the learning effects from repeated administration of the neurocognitive tests. The surgical and nonsurgical groups were similar in gender, education level, computer use familiarity, and baseline MMSE-2 score. The two groups were different in age marginally in favor of the nonsurgical group, and in race as the surgical group had larger proportion of White subjects. There was no difference between the two groups in depression status and sleep quality scores at baseline or follow-up. Within each group, there was no difference in depression status and sleep quality scores between baseline and follow-up. Using the *Z*-score method, we identified 11 (15.9%) patients with POCD in the surgical group. Multivariable logistic regression analysis using Firth's method showed that carrying the ApoE4 allele (at least one allele), using one or more highly anticholinergic or sedative-hypnotic medications at home prior to surgery, and receiving sevoflurane for anesthesia were predictors of the development of POCD.

CHAPTER 6: DISCUSSION

I. INCIDENCE OF POCD

The results of this study showed that about 16% of study subjects were identified with POCD three months after elective major noncardiac surgery. A major difficulty of all POCD studies is the comparability of POCD incidence between different studies, as this depends largely on how POCD was defined and what was considered as 'sufficient' decline in cognitive function after surgery in each study. Also, this varies by the time of postoperative assessment of cognitive function. Several studies overestimated the incidence of POCD by evaluating it during the first week after surgery when the patient is still having pain, in recovery from anesthesia, and under the influence of several postoperative analgesics. The incidence will also depends on whether the study has a control group to adjust for learning effects that occur from repeated administration of neurocognitive tests.

In our study, we used the most stringent definition of POCD that is dependent on the *Z*-score method originally used by the ISPOCD group, and we also used a control group to adjust for learning effects.[1] However, the use of POCD as a dichotomous variable (yes or no) has its limitations as well particularly it decreases the power of the study as compared to defining it as a continuous variable by assessing mean score change in study subjects. However, the use of mean score change in POCD studies is not recommended because learning effects are disregarded, and the individual change is thereby not assessed. Instead, the definition of POCD should be based on comparing preoperative with postoperative test results for each patient. The *Z*-score method provides us with information about the expected improvement over time in the surgical group by looking at the change in the nonsurgical control group. This definition corrects for this learning

effect and eliminates the risk that a true deterioration in cognitive function may be overlooked in the surgical group.

Newman et al. conducted a meta-analysis of POCD studies in noncardiac surgery until December 2005 showing that the incidence of POCD was 6.2% - 56% after major noncardiac surgery when assessed 22 days and up to six months after surgery.[2] When ignoring one of the studies included in the meta-analysis with unexpectedly very high incidence, the incidence of POCD was between 6.2% - 9.4%.[2] The incidence of POCD in our study is in agreement with the incidence reported in the first ISPOCD study which was about 10%.[1] Monk et al. conducted a study in 1064 patients, 308 of which were in a group aged 60 years or older.[3] Three months after surgery, the incidence of POCD was 12.7% in this group of older patients, which is comparable to the percentage of POCD in our study.[3] Koch et al. reported a POCD incidence of 45% three months after surgery in a group of 24 patients aged 65 years or older who underwent elective knee or hip replacement.[4] The incidence reported in this study is very high compared to our study. However, though this study used robust measures for neuropsychological testing, their definition of POCD was very arbitrary and is not the currently acceptable definition in POCD research that was established by the first ISPOCD study. Koch et al. used a definition of at least 20% decline from baseline in two or more tests which could result in the overestimated incidence of POCD. Evered et al. conducted a very recent study in 644 patients, 157 of which were 55 years and older, who underwent total hip joint replacement.[5] They reported a POCD incidence of 16% three months after surgery which is also in agreement of the incidence in our study.[5] Deo et al. conducted a study in two groups of patients undergoing knee replacement with age ranging from 43 to 82 years old, and they compared the incidence of POCD in the two groups using two different surgery techniques.[6] They found a similar POCD incidence of about 30% six months

after surgery in both groups.[6] This high incidence of POCD in this study may be also be a result of using a less stringent approach in diagnosing POCD (0.5 SD decline in at least three cognitive tests).[6]

Our study used a robust computerized neurocognitive battery that is valid and reliable, and is designed specifically to evaluate subtle changes in cognitive function over time. The battery measures several cognitive domains that were recommended by consensus guidelines for evaluation of POCD.[7] The battery was also validated in volunteers with several age groups ranging from seven to ninety years old, which includes the age range for our study patients.[8] We used a control group that is similar to the surgical patients in age, education level, and computer use familiarity along with the use of parallel forms in the neurocognitive battery to prevent or minimize learning effects to the most degree possible. In addition to that, we used the currently established *Z*-score method for identifying patients with POCD. This definition that was originally used in the first ISPOCD study is robust and it also adjusts for any learning effects from repeated administration of the cognitive tests to provide a reasonably accurate estimate of POCD incidence.

It is also very important to note that we acknowledged the fact that depression and poor sleep quality can negatively affect performance on neuropsychological testing, and we evaluated the depression status and sleep quality for the surgical and nonsurgical groups at baseline and follow-up to make sure there was no variability in depression status or sleep quality within and between the two groups that could have affected their performance differently on cognitive tests, and consequently the incidence of POCD. Our decision to evaluate the incidence of POCD three months after surgery was based on the overestimated incidence observed in several studies that evaluated POCD too soon after surgery and reported an inflated incidence of POCD. Even if a

the high incidence of POCD reported in some studies shortly after surgery represents a true deterioration, we chose to evaluate long-term cognitive outcomes which is more important to patients and their caregivers than changes that nay occur immediately in the short period after surgery and become reversible soon after hospital discharge. The incidence reported in our study supports the fact that POCD does exist in older adults three months after major elective noncardiac surgery with an incidence of about 16% when assessed using robust neuropsychological tests and defined using the *Z*-score method with the involvement of a nonsurgical control group to adjust for the learning effects.

II. RISK FACTORS FOR POCD

The multivariable analysis in our study showed that risk factors for POCD were carrying the ApoE4 allele, using one or more drugs with highly anticholinergic or sedative-hypnotic properties at home prior to surgery, and receiving sevoflurane for anesthesia. The current evidence in the literature about the association between these risk factors and POCD is still lacking and conflicting.

In our study, the percentage of patients identified with POCD who had the ApoE4 allele was 35.7% compared to 11.3% who did not have the allele. Carrying the ApoE4 allele was associated with POCD three months after major noncardiac surgery in our study. This is not in agreement with the investigation by Abildstrom et al. who conducted a multicenter study in a total of 976 patients aged 40 years and older undergoing noncardiac surgery and could not find a difference in the incidence of POCD three months after surgery in patients with and without the ApoE4 allele (ApoE4 = 10.3%, non-ApoE4 = 8.4%; $p = 0.40$).[9] However, the statistical power of this study was limited because of the lower incidence of POCD than expected and they also

included patients who are much younger than our patient group.[9] The same finding was reported by McDonagh et al. who conducted a study in 394 patients older than 55 years old who underwent major noncardiac surgery.[10] When they evaluated POCD one year after surgery in 291 subjects, they could not find an association between ApoE4 genotype and POCD (ApoE4 = 45.9%, non-APOE4 = 46.3%; $p = 0.95$).[10] However, this study had an exaggerated incidence of POCD due to using a more liberal arbitrary definition of POCD. A recent study by Cai et al. showed an association of POCD with ApoE4 genotype three days after noncardiac surgery.[11] However, they used MMSE in identifying patients with POCD, which is no longer an accepted method to diagnose POCD or evaluate any changes in cognitive function in general. MMSE is only a screening instrument for dementia and, alone, cannot yield a diagnosis of dementia or cognitive problems.[12] The mechanism by which ApoE4 may cause detrimental cognitive outcomes is still unclear.[10] Potential etiologies include the specific effects on cerebral blood flow, altered responses to neuronal injury, cerebral metabolic decline, and increased cerebral microemboli secondary to increased atheroma burden.[10] Also, there is support from several studies that ApoE4 may be linked to the inflammatory response to injury that may occur during surgery.[10] ApoE4 can modulate this response by modifying glial activation, nitric oxide production, inflammatory cytokine production, and magnitude of cerebral edema.[10] The association of ApoE4 gene with both POCD and AD can suggest that these two conditions may share similar mechanisms through β-amyloid and tau phosphorylation formation.[13]

Our study is the first to investigate the association between using highly anticholinergic or sedative-hypnotic drugs at home prior to surgery and the risk of POCD three months after major noncardiac surgery. We only considered highly anticholinergic and sedative-hypnotic medications that have been included in the 2012 American Geriatrics Society updated Beers

criteria for potentially inappropriate medication use in older adults, as they are supported with strong evidence to cause harmful cognitive outcomes in older adults.[14] Also, the anticholinergic drugs included in the list are only those with strong anticholinergic properties compiled from the Anticholinergic Risk Scale, Anticholinergic Drug Scale, and Anticholinergic Burden Scale which makes this list comprehensive.[14] Highly anticholinergic drugs have been known for a long time to have negative cognitive outcomes especially in the older adult population.[15-17] Carrière et al. studied a population-based cohort of 4128 women and 2784 men recruited from three French cities who had their cognitive function, clinical diagnosis of dementia, and anticholinergic evaluated at baseline, two, and four years later.[18] The study found that older adults who were taking anticholinergic drugs were at increased risk for cognitive decline and dementia, and discontinuing anticholinergic drugs was associated with a decreased risk.[18] Interestingly, there was an interaction between the use of anticholinergic drugs in women and carrying the ApoE4 allele exposing patients with both to higher risk of cognitive dysfunction and dementia.[18] Cai et al. conducted a retrospective cohort study with one-year follow-up of cognitive function in 3690 older adults finding that the odds ratio for having a diagnosis of mild cognitive impairment (MCI) was 2.73 (1.27–5.87) among older adults who were exposed to three or more possible anticholinergic drugs for at least 90 days.[19] Also, the long-term use of sedative-hypnotics, particularly benzodiazepines, is a risk factor for increased cognitive decline in older adults.[20,21]

The cumulative burden of using these drugs at home prior to surgery can put the patients at higher risk to the insult from the surgery and anesthesia, which may expedite the progression of cognitive deterioration and make it more prominent few months after surgery. Our study showed that patients who were using at least one highly anticholinergic or sedative-hypnotic medications at home before surgery were at higher risk for POCD three months after surgery.

The reason we categorized the use of anticholinergic and sedative medications into only two groups (nonuse, and using one or more medications of this group) is that, with the exception of one patient who was using three medications and another who was using four medications of this group, all other patients were either nonusers or users of only one anticholinergic or sedative-hypnotic medications.

There is a growing interest in the involvement of individual anesthetic agents in the etiology of POCD. In our study, we compared the risk of POCD associated with the use of each individual anesthetic agent in study patients. The results showed that the use of sevoflurane for anesthesia was associated with higher risk of POCD three months after major noncardiac surgery. The relationship between sevoflurane and POCD or cognitive decline in general is still debatable. A study by Dong et al. showed that sevoflurane can induce apoptosis and increase β-amyloid protein levels in mice which suggests that sevoflurane may promote AD neuropathogenesis.[22] Le Freche et al. reached a similar conclusion when they demonstrated that sevoflurane exposure was associated with increased tau-phosphorylation and spatial memory deficits in mice one month after surgery.[23] In this study, cognitive deterioration was transient at the first exposure to sevoflurane, but it became permanent with repeated exposure to the anesthetic agent.[23] Liu et al. conducted a prospective, randomized parallel-group study in 180 patients aged 65 to 75 years old with amnestic mild cognitive impairment, a subtype of mild cognitive impairment in which memory loss is the predominant symptom, who were randomly assigned to a sevoflurane, propofol or lidocaine epidural anesthesia group (n = 60 per group) during spinal surgery.[24] They assessed patients' cognitive function before and two years after surgery and obtained a cerebrospinal fluid sample by lumbar puncture from patients before the end of the surgery.[24] They found that the number of cases who had progressive mild cognitive

impairment was greater in the sevoflurane group, and not the propofol or lidocaine groups, than in the control group.[24] Patients who developed progressive amnestic mild cognitive impairment had increased total tau and increased phosphorylated tau levels compared with those with stable mild cognitive impairment and the control group.[24] On the other hand, sevoflurane has been suggested to have a protective effects on long-term cognitive function of Wistar rats by suppressing the inflammatory responses that occur during surgery.[25] However, it is still unknown if these findings can be applied to humans, and whether the duration of anesthesia can play a role in changing the neuroprotective effect of sevoflurane during surgery to a detrimental effect on cognitive function with extended exposure. Kadoi et al. conducted a retrospective study on 109 patients to test whether sevoflurane anesthesia had any ameliorative effects on POCD after CABG surgery.[26] However, they could not find a significant association between POCD six months after surgery and the use of sevoflurane.[26] These studies show that most of the research about the relationship between sevoflurane and the risk of cognitive deterioration conducted in humans reported either a protective effect or no difference in the risk between sevoflurane and other anesthetics agents. However, recent studies in animals showed significant and dose-dependent deterioration of cognitive function with the use of sevoflurane. This warrants a need for further studies to compare the risk of POCD associated with the use of sevoflurane and other anesthetic agents in humans at variable doses and duration of exposure, and to confirm the possible tau phosphorylation mechanism by which sevoflurane might be causing cognitive deterioration after surgery.

III. STUDY LIMITATIONS

A major limitation of all studies investigating the incidence and risk factors of POCD is that there are major differences in research methodologies, including the neurocognitive batteries

used, the time interval between preoperative and postoperative assessment, and the definition and statistical methods used to identify patients with POCD. We used a robust study design that is consistent with the most recent guidelines and methodology of large studies particularly the ISPOCD studies allowing us to compare our findings with the findings of other well-designed studies. However, our study was limited by the small sample size due to the prospective nature of the study and the limited time and funding we had to recruit enough subjects. Despite the small sample size, we could still find a POCD incidence of 16% in our study subjects and this incidence is in agreement with current investigations of POCD after noncardiac surgery with robust methodology.

One of the limitations of observational studies is that they can only identify associations, and not causality, between independent variables and the outcome of interest. Due to the observational nature of our study, it is possible that the association we found between POCD three months after major noncardiac surgery and carrying the ApoE4 allele, using at least one highly anticholinergic or sedative-hypnotic drug prior to surgery, and receiving sevoflurane for anesthesia was due to chance. An alternative explanation of the results or other underlying causes for POCD may exist. In order to confirm a cause-and-effect relationship between these risk factors and long-term POCD, randomized-controlled trials should be conducted.

We had to conduct some of the follow-up cognitive testing sessions for patients in both surgical and nonsurgical groups at their residence if they were not willing to come back to the hospital. Theoretically, this could have affected the results of the study by performing the follow-up cognitive testing at two different environments assuming that the hospital environment may be more stressful to study subjects compared to their own residence. However, we always recommended that patients do the follow-up testing at the hospital and we did not choose which

patients do the follow-up testing at their residence, and it was randomly based on the willingness of patients to come back to the hospital. However, we did not want to risk losing patients at follow-up in addition to the fact that cognitive testing done at the hospital was conducted in a very quiet private room with no distractions at all which may simulate patient's home environment.

Pain and anxiety can negatively affect performance of patients on neurocognitive testing and may cause them to be less motivated or focused on the test. Patients in the surgical group probably had pain and anxiety before the surgery during baseline cognitive testing. The level of pain and anxiety could have changed, probably decreased, by the time of follow-up testing three month after surgery which could have led to improvement of their performance on the tests. We did not assess the level of pain or anxiety at baseline or follow-up, and we do not know if this had an effect on the results of cognitive tests. We thought it would be too much burden and time-consuming to assess pain and anxiety in addition to depression and sleep quality before each testing session. Conducting an extensive battery of tests can discourage many patients from participation in research. If not evaluating pain and anxiety before each testing session has caused any error, it would have underestimated the incidence of POCD in our study, because patients would be expected to have improved performance on cognitive tests.

A large percentage of subjects in the patient and control groups refused to participate in the study. We do not have information about those who refused to participate since they did not sign the consent form. However, it is concerning whether the demographics and characteristics of subjects who did not participate in the study might be different from those who were included in the study. It is often the very old and more fragile patients who refuse to participate in studies like this particularly if they might be concerned about their cognitive function and they prefer not

to know about it. Some patients may also have very low educational level that they might be concerned about their ability to perform well on cognitive testing and the embarrassment they might experience especially with a computerized battery like the one in our study. We would expect to see a higher incidence of POCD if such patients were involved in the study.

There was a higher representation of subjects with lower education level in the control group than the patient group, though the difference between the two groups in education level was not statistically significant. This difference could lead to different performance on cognitive testing resulting in a difference in the magnitude of learning effects that occur in controls as compared to patients, and consequently a potential bias in the incidence of POCD in the surgical group.

Due to the small sample size, we had to combine anticholinergic and sedative-hypnotic drugs in one category. We also were not able to tests the relationship between the total drug burden taking into consideration the dose and regimen due to the small sample size.

IV. FUTURE DIRECTIONS

Future research should be directed towards conducting multicenter studies with larger samples, more diverse population, and expanded types of major noncardiac surgery to increase generalizability. Also, with appropriate funding and enough time, POCD should be assessed several times over a longer period of time to capture the changes that occur to the cognitive function of study subjects, and determine if POCD is a temporary or rather a permanent condition. Also, it would be interesting to determine if there is an association between POCD and AD since ApoE4 genotype has been associated with both conditions. The inflammatory theory has a great potential to explain the etiology of POCD. However, we were not able to

determine whether this is true in our study because we measured only one inflammatory biomarker and only once before surgery without postoperative evaluation. We were testing the hypothesis if patients with preoperative heightened inflammatory response may be at higher risk for POCD three months after noncardiac surgery. However, it would be actually more promising to test the hypothesis that patients who develop an inflammatory response during surgery may be at higher risk for POCD by measuring the blood levels of more than one inflammatory biomarkers that may play a role in the etiology of POCD (e.g., CRP, IL-1, IL-6, IL-8, TNF-alpha) before and several times immediately after surgery at short intervals for at least 72 hours especially that we do not know yet when each of these markers peaks in blood levels after being released as an active response to inflammation during surgery. Our finding that using one or more highly anticholinergic or sedative-hypnotic medications at home prior to surgery was associated with POCD warrants future investigation of this relationship taking into consideration the dose and duration of use of each of these medications. It might be also interesting to investigate if discontinuing these drugs for a certain duration before surgery may decrease the risk of POCD after surgery. Also, future research can investigate the possible protective effect of certain anti-inflammatory drugs in decreasing the risk of POCD in patients undergoing different types of surgery and anesthesia. Our finding that sevoflurane was associated with POCD warrants further investigations by using randomized controlled trials comparing sevoflurane with other general anesthetics to make a definitive conclusion whether sevoflurane causes POCD, and if it does, whether it positions the patient at higher risk than other general anesthetics. It also important to further investigate the mechanism by which sevoflurane might be causing cognitive decline after surgery, and whether the tau phosphorylation theory is valid.

V. CONCLUSION

POCD was present in about 16% of older adult patients three months after elective major noncardiac surgery. Carrying the ApoE4 allele, using one or more highly anticholinergic or sedative-hypnotic drugs prior to surgery, and receiving sevoflurane for anesthesia were risk factors for long-term POCD. Suggestions for future research in this area include using larger sample in a multicenter study, studying the association between the change in blood levels of several potential inflammatory biomarkers before and after surgery and its association with POCD, investigating the relationship between POCD and AD, studying the effect of dose and duration of use of anticholinergic and sedative-hypnotic medications before surgery on the risk of POCD, and investigating the protective effect of certain anti-inflammatory on decreasing the risk of POCD in older adults after different types of surgery and anesthesia.

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APPENDIX A

Approved Consent form for Study Surgical Group

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Risk Factors for the Development of Postoperative Cognitive Dysfunction in Older Adults Undergoing Major Noncardiac Surgery

VCU IRB PROTOCOL NUMBER: HM13608

INVESTIGATORS:

Patricia W. Slattum, PharmD, PhD
Associate Professor and Director of Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science
VCU School of Pharmacy

Clarence J. Biddle, CRNA, PhD
Professor and Director of Research
Department of Nurse Anesthesia
VCU School of Allied Health Professions

Osama A. Shoair, BPharm
PhD Candidate, Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science
VCU School of Pharmacy

This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this study is to determine how often cognitive changes, such as changes in memory, attention, information processing speed, reaction time, and mental flexibility, occur after elective orthopedic surgery or neurosurgery in individuals 65 years or older and what the risk factors are for increasing the likelihood of developing such cognitive changes after these surgeries. Also, a secondary analysis will be done on the data collected to evaluate if there is a relationship between older patients' medications and diseases and their cognitive function.

DESCRIPTION OF THE STUDY

Before surgery, we will use computerized tests to evaluate your cognitive function, depression status, and quality of sleep. After surgery, we will test you to see if you have delirium (an acute condition that is characterized by feeling of confusion, difficulty in focusing, paying attention, or organizing thoughts) that can possibly happen in some individuals 24 – 36 hours after surgery. At discharge from the hospital, we will measure your cognitive function again using another set of computerized tests. Finally, we will evaluate your cognitive function, depression status, and sleep quality again 3 months after surgery and this will conclude the study.

In addition to computerized testing, you may opt to provide a 5-mL blood sample before surgery for genetic testing that may help in the future to identify if there is a relationship between certain genes and development of cognitive changes in individuals 65 years and older after elective orthopedic surgery or neurosurgery.

You may also opt to provide a 5-mL blood sample before surgery for testing of an inflammatory biomarker that may help in the future to identify if there is a relationship between preoperative high level of this biomarker and development of cognitive changes in individuals 65 years and older after elective orthopedic surgery or neurosurgery.

Information about you and your surgical procedure, including but not limited to, age, sex, race, weight, height, educational level, alcohol intake, smoking status, previous surgeries, health conditions, current medications, type and duration of anesthesia, duration of surgery, and other surgical details will be collected from your medical records and evaluated in this study.

Your participation in this study will last for up to 3 months after your surgery. Approximately 150 subjects will participate in this study.

Significant new findings developed during the course of this research which may relate to your willingness to continue participation will be provided to you.

PROCEDURES

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered.

During your visit to the preoperative assessment clinic, one of the study investigators will collect the following information about you: demographics, age/date of birth, sex, race/ethnicity, weight, height, educational level, computer familiarity, diagnosis on admission, previous/future surgeries, current medications, health conditions, smoking status, and alcohol consumption. He will also do a simple screening cognitive test to determine your eligibility for the study. This part will take about 30 minutes to complete. If you are eligible to participate in the study, one of the study investigators will evaluate your cognitive function, depression status, and sleep quality using a computer test that will take about 30 minutes to complete.

If you choose to provide a blood sample for testing of genetic and/or inflammatory biomarkers, two 5-mL blood samples will be withdrawn from you on the day of the surgery just before the induction of the anesthesia from the intravenous line that you will have by that time. Your privacy will be protected by storing your blood samples labeled with a barcode that does not contain your name or any personal information. Your personal information will be stored in a secure computer database at VCU.

After your surgery and while you are still in the hospital, one test will be administered at 24 – 36 hours after surgery to evaluate if you have delirium (an acute condition that is characterized by feeling of confusion, difficulty in focusing, paying attention, or organizing thoughts) after surgery. This test should take from 5 – 15 minutes to complete. Also, another set of cognitive tests will be administered at discharge from the hospital that should take about 30 minutes to complete. Information about your surgical procedure, including but not limited to, type and duration of anesthesia, duration of surgery, medications administered during surgery, and other surgical details will be obtained from your surgical record.

Approximately 3 months after your surgery, another set of tests that measures your cognitive function, depression status, and sleep quality will be administered and should take about 30 minutes. These measurements may take place at your doctor's office during a regularly scheduled visit or at your residence.

RISKS AND DISCOMFORTS

The computerized tests of cognitive function, depression status, and sleep quality that you will take require only about 30 minutes per session to complete. The tests will be conducted in a private quiet room at Virginia Commonwealth University Health System (VCUHS) where you feel comfortable.

If you opt to provide a blood sample for genetic analysis, only 5-mL (one teaspoonful) of blood will be withdrawn from you on the day of the surgery just before the induction of the anesthesia. Risks of blood drawing (venipuncture) include bleeding, bruising, and fainting.

If you opt to provide a blood sample for biomarker analysis, only 5-mL (one teaspoonful) of blood will be withdrawn from you on the day of the surgery just before the induction of the anesthesia. Risks of blood drawing (venipuncture) include bleeding, bruising, and fainting.

The tests you will take at each session may show that you are having depression and/or poor sleep quality. In either case, we will let you know immediately after the testing session and encourage you to seek help from your primary care physician.

There is also a minimal risk of transmitting your personal identifying information to persons not on the study team. However, we minimize this risk by immediately de-identifying this information once we collect it from you and keeping it in a secure place that only study personnel have access to.

BENEFITS TO YOU AND OTHERS

There is no direct benefit to you for participating in this study, but what is learned from this study may help other individuals undergoing elective orthopedic surgery or neurosurgery in the future identify, minimize, or prevent their risk for developing cognitive decline after these types of surgery and to understand the relationship between older patients' medications and diseases and their cognitive function.

If we find that your cognitive function appears to change during the study, you have experienced depression, or if you are concerned about your cognitive function or depression test results, the investigators will inform you and encourage you to see your primary care physician for further evaluation.

COSTS

There are no charges at all for the study visits, or any cognitive, depression, or sleep quality tests. There is also no cost at you to do blood genetic and/or biomarker testing if you opt to provide blood samples for the purpose of conducting these tests.

PAYMENT FOR PARTICIPATION

You will receive a $25 VISA® gift card for completing the first set of cognitive function, depression status, and sleep quality tests before your surgery. You will receive an additional $25 VISA® gift card for completing the confusion test 24 – 36 hours after surgery and the second set of cognitive tests at discharge. You will receive a $50 VISA® gift card after the third set of cognitive function, depression status, and sleep quality tests at 3 months after surgery for a total of $100 in the form of VISA® gift cards if you completed all the study assessments. VISA® gift cards can be used wherever VISA® debit cards are accepted. The cards cannot be reloaded or used at ATM machines for cash withdrawals.

ALTERNATIVE

Your alternative is not to participate in this study.

CONFIDENTIALITY

Potentially identifiable information about you will consist of results from cognitive function, depression status, sleep quality tests, and data abstracted from your medical record. This data is being collected solely for research purposes. The data from cognitive function, depression status, and sleep quality tests will be securely stored separately from medical records in a locked research area and a secured computerized database at VCU.

If you opt to provide blood samples for genetic and/or biomarker testing, they will be securely stored at VCU School of Pharmacy. All personal identifying information will be kept in password-protected files. Access to all data will be limited to study personnel who have undergone special training on maintaining confidentiality of individuals participating in research.

You should know that research data or medical information about you may be reviewed or copied by Virginia Commonwealth University. Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

DATA FROM COGNITIVE FUNCTION, DEPRESSION STATUS AND SLEEP QUALITY TESTING AND MEDICAL RECORD DATA

I give permission for my data from cognitive function, depression status and sleep quality testing, and data from my medical record collected in this study to be stored and used for research related to cognitive impairment in older adults, including but not limited to, postoperative cognitive dysfunction and Alzheimer's disease.

☐ Yes

☐ Yes, but I want to be contacted prior to any future use of my data for research

☐ No

GENETIC TESTING

I opt to provide a 5-mL blood sample before surgery for genetic testing related to this research. I understand that study investigators will not disclose individual test results to me or any other third party.

☐ Yes

☐ No

I give permission for my genetic testing results to be stored and used for future research related to cognitive impairment in older adults, including but not limited to, postoperative cognitive dysfunction and Alzheimer's disease.

☐ Yes

☐ Yes, but I want to be contacted prior to any future use of my data for research

☐ No

BIOMARKER TESTING

I opt to provide a 5-mL blood sample before surgery for testing of inflammatory biomarkers related to this research. I understand that study investigators will not disclose individual test results to me or any other third party.

☐ Yes

☐ No

I give permission for my biological markers testing results to be stored and used for future research related to cognitive impairment in older adults, including but not limited to, postoperative cognitive dysfunction and Alzheimer's disease.

☐ Yes

☐ Yes, but I want to be contacted prior to any future use of my data for research

☐ No

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled.

If you do participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled. You may also choose to participate in the study but not provide blood samples for genetic and/or biomarker testing. Your decision to participate in the study but not to provide blood samples will involve no penalty or loss of benefits to which you are otherwise entitled.

Your participation in this study may be stopped at any time without your consent. The reasons might include, but not limited to, that you have not followed study instructions, there are administrative reasons that require your withdrawal, or that we have stopped the study.

QUESTIONS

In the future, you may have questions about your study participation. If you have any questions, complaints, or concerns about the research, contact:

Patricia W. Slattum, PharmD, PhD
Director, Geriatric Pharmacotherapy Program
Virginia Commonwealth University

410 N 12th Street, Smith Building, Room 656A
Richmond, VA 23298-0533
PO Box 980533
(804) 828-6355

If you have questions about your rights as a research subject, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 113
PO Box 980568
Richmond, VA 23298
(804) 827-2157

You may also contact this number for general questions, concerns or complaints about the research. Please, call this number if you cannot reach the research team or wish to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. Additional information about participation in research studies can be found at http://www.research.vcu.edu/irb/volunteers.htm.

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____

Subject Name, printed Subject Signature Date

_____

Name of Person Conducting Informed Consent
Discussion / Witness
(Printed)

_____ _____

Signature of Person Conducting Informed Consent Date
Discussion / Witness

_____ _____

Principal Investigator Signature (if different from above) Date

APPENDIX B

Approved Consent form for Study Nonsurgical Group

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Risk Factors for the Development of Postoperative Cognitive Dysfunction in Older Adults Undergoing Major Noncardiac Surgery

VCU IRB PROTOCOL NUMBER: HM13608

INVESTIGATORS:

Patricia W. Slattum, PharmD, PhD
Associate Professor and Director of Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science
VCU School of Pharmacy

Clarence J. Biddle, CRNA, PhD
Professor and Director of Research
Department of Nurse Anesthesia
VCU School of Allied Health Professions

Osama A. Shoair, BPharm
PhD Candidate, Geriatric Pharmacotherapy Program
Department of Pharmacotherapy and Outcomes Science
VCU School of Pharmacy

This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this study is to determine how often cognitive changes, such as changes in memory, attention, information processing speed, reaction time, and mental flexibility, occur after elective orthopedic surgery or neurosurgery in patients 65 years and older and to identify the risk factors for increasing the likelihood of such cognitive changes after these surgeries. Also, a secondary analysis will be done on the data collected to evaluate if there is a relationship between older patients' medications and diseases and their cognitive function.

In order to accurately measure changes in cognitive function in older patients undergoing surgery in our study, we need to recruit a control group of older adults who are not undergoing surgery

within 3 months and measure their cognitive function at the same time interval as the patients in our study (baseline and 3 months later) to compare the change in cognitive function between the patient and control groups.

DESCRIPTION OF THE STUDY

We will use a computer program called CNS Vital Signs™ to assess your cognitive function, depression status, and sleep quality at your first meeting with us and again 3 months later to see if there is any significant change in your cognitive function. It will take about 30 minutes to complete all the tests at each of the two sessions. These tests may take place at your residence or at a private quiet room at VCU Health System.

Your participation in this study will last for about 3 months after your first interview with the study team. Approximately 100 subjects will participate in this study as controls. Significant new findings developed during the course of this research which may relate to your willingness to continue participation will be provided to you.

PROCEDURES

If you decide to be in this research study as a control, you will be asked to sign this consent form after you have had all your questions answered.

If you decide to be part of the study, the research team will conduct their first interview with you either at VCU Health System or at your residence. During this first interview, the study investigators will collect information about your age, gender, race, education level, computer familiarity, smoking status, alcohol consumption, health conditions, future surgeries, and current medications.

We will also do a simple screening cognitive test to determine your eligibility for the study. If you are eligible to participate in the study, one of the study investigators will evaluate your cognitive function, depression status, and sleep quality using a computer test that will take about 30 minutes to complete.

Approximately 3 months after your first interview, we will arrange another meeting with you at VCU Health System or at your residence to evaluate your cognitive function, depression status, and sleep quality again using the same tests from the first interview which will take about 30 minutes to complete. We will also check if there has been any change to your current medications.

RISKS AND DISCOMFORTS

The computerized tests of cognitive function, depression status, and sleep quality that you will take require only about 30 minutes per session to complete. The tests will be conducted in a

private quiet room at VCU Health System or your residence where you feel comfortable. There are times in between different tests when you can take a break if you want to. If you feel exhausted at any time, you can stop the testing session.

The tests you will take at each session may show that you are having depression and/or poor sleep quality. In either case, we will let you know immediately after the testing session and encourage you to seek help from your primary care physician.

There is also a minimal risk of transmitting your personal identifying information to persons not on the study team. However, we minimize this risk by immediately de-identifying this information once we collect it from you and keeping it in a secure place that only study personnel have access to.

BENEFITS TO YOU AND OTHERS

There is no direct benefit to you for participating in this study, but what is learned from this study by comparing the change in cognitive function between study patients and controls from baseline to the 3-month follow-up may help in the future to minimize or prevent the risk for developing cognitive decline after elective orthopedic surgery or neurosurgery in older adults and to understand the relationship between older patients' medications and diseases and their cognitive function.

If the cognitive screening test shows that you have a cognitive problem or if we find that you may have depression or poor sleep quality, the study investigators will inform you and encourage you to talk to your primary care physician for further evaluation.

COSTS

There are no charges at all for the study visits, or any cognitive, depression, or sleep quality tests.

PAYMENT FOR PARTICIPATION

You will receive a $25 VISA® gift card for completing the cognitive function, depression status, and sleep quality tests at your first interview. You will receive an additional $50 VISA® gift cards for completing the cognitive function, depression status, and sleep quality tests at your second interview for a total of $75 in the form of VISA® gift cards if you complete both study assessments. VISA® gift cards can be used wherever VISA® debit cards are accepted. The cards cannot be reloaded or used at ATM machines for cash withdrawals.

ALTERNATIVE

Your alternative is not to participate in this study.

CONFIDENTIALITY

Information about your age, gender, race, education level, computer familiarity, smoking status, alcohol consumption, health conditions, future surgeries, and current medications in addition to your results of cognitive function, depression status, and sleep quality tests is being collected solely for research purposes. This data will be securely stored in a locked research area and a secured computerized database at VCU. Access to all data will be limited to study personnel who have undergone special training on maintaining confidentiality of individuals participating in research.

You should know that research data or medical information about you may be reviewed or copied by Virginia Commonwealth University. Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed.

FUTURE USE OF DATA

I give permission for my data collected in this study to be stored and used for research related to cognitive impairment in older adults. (Please, check and initial your choice)

☐ Yes _____

☐ Yes, but I want to be contacted prior to any future use of my data for research _____

☐ No _____

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits you are otherwise entitled to.

Your participation in this study may be stopped at any time without your consent. The reasons might include, limited to, that you have not followed study instructions, there are administrative reasons that require your withdrawal, or that we have stopped the study.

QUESTIONS

In the future, you may have questions about your study participation. If you have any questions, complaints, or concerns about the research, contact the study principal investigator:

Patricia W. Slattum, PharmD, PhD
Director, Geriatric Pharmacotherapy Program

Virginia Commonwealth University
410 N. 12th Street, Smith Building, Room 656A, P.O. Box 980533
Richmond, VA 23298-0533
(804) 828-6355
If you have questions about your rights as a research subject, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 113
PO Box 980568
Richmond, VA 23298
(804) 827-2157

You may also contact this number for general questions, concerns or complaints about the research. Please, call this number if you cannot reach the research team or wish to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. Additional information about participation in research studies can be found at http://www.research.vcu.edu/irb/volunteers.htm

CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I can request a copy of the signed consent form once I have agreed to participate.

_____

Subject Name, printed Subject Signature Date

_____

Name of Person Conducting Informed Consent
Discussion / Witness
(Printed)

_____ _____

Signature of Person Conducting Informed Consent Date
Discussion / Witness

_____ _____

Principal Investigator Signature (if different from above) Date

Vita

Osama Ali Shoair was born on August 27, 1983 in Cairo, Egypt, and is an Egyptian citizen. He received his Bachelors of Pharmaceutical Sciences with Honors from Misr International University, Cairo, Egypt in 2005. Immediately after graduation, Osama was invited to teach in the School of Pharmacy at Misr International University. Osama received a Certificate in Aging Studies from Virginia Commonwealth University, Richmond, Virginia in 2013. He also completed the Preparing Future Faculty program at Virginia Commonwealth University and received the Certificate of Teaching Excellence at the conclusion of the program. Osama published a review article as a first author on medication-related dizziness in older adults in addition to several abstracts about the risk factors for postoperative cognitive dysfunction in older adults undergoing major noncardiac surgery. Osama's research interest is focused on medication-related problems in older adults.